

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

2-MERCAPTOBENZOTHIAZOLE, SODIUM SALT

Chemical Code # 000613, Tolerance # 50820  
SB 950 # 868  
November 19, 2003

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study on file.
Subchronic rat (Dermal):	No data gap, no adverse effect
Chronic toxicity, dog:	Data gap, no study on file.
Oncogenicity, rat:	Data gap, inadequate study, possible adverse effect indicated.
Oncogenicity, mouse:	Data gap, inadequate study, possible adverse effect indicated (females).
Reproduction, rat:	No data gap, possible adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	Data gap, no study on file.
Gene mutation:	No data gap, possible adverse effect indicated (in summary data).
Chromosome effects:	No data gap, possible adverse effects (in summary data).
DNA damage:	Data gap, inadequate study, no adverse effect indicated.
Neurotoxicity:	Not required at this time.

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Toxicology one-liners are attached.

All record numbers through 125448 were examined.

\*\* indicates an acceptable study.

**Bold face** indicates a possible adverse effect.

File name: T031119

Prepared by H. Green and Gee, 11/19/03

The US EPA issued a "Reregistration Eligibility Decision (RED): Sodium and Zinc Salts of 2-Mercaptobenzothiazole" in September of 1994. At that time, no additional data requirements were identified for studies addressing health effects studies under SB950. The sodium salt had no pesticidal food uses at that time. The RfD for 2-mercaptobenzothiazole was determined to be 0.65

mg/kg/day. This was based on the rat reproductive study with a systemic NOEL of 2500 ppm (194 mg/kg/day) for lower body weight, an uncertainty factor of 100 with an additional safety factor of 3, based on the lack of chronic toxicity data in a non-rodent species. The MOE calculated by US EPA was 47,000 for occupational risk, based on a NOEL of 200 mg/kg/day from a dermal study. The zinc salt is not currently registered in California. (Gee, 10/9/03)

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

### CHRONIC TOXICITY, RAT

Data gap, no study on file.

#### Subchronic rat

No record number or volume number. "Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)." (Dieter, M. P., Physiological Research Laboratories, Minneapolis, Minnesota, NTP TR 332, NIH Publication No. 88-2588, May 1988). 2-Mercaptobenzothiazole (lot V10479, purity of 96%) was given by oral gavage to 10/sex/group at doses of 0 (corn oil), 188, 375, 750 or 1500 mg/kg/day, 5 days per week for 13 weeks. In a previous study, all animals died at 3000 mg/kg/day. Animals were observed twice daily and weighed weekly. Necropsy was performed on all animals; histology exams were performed on selected animals from all groups with most tissues included. No treatment-related deaths occurred. Irritable behavior was more pronounced with increasing dose and characterized as resistance to gavage - no data. Body weight gain was lower in males by 15% and by 14% in females. Total body weights were lower in males at  $\geq 375$  mg/kg and in all groups of females. Absolute and relative liver weights were increased at all doses, with relative weights being statistically significant in both sexes at all doses. A statement was made that there were no gross or microscopic findings related to treatment - no data. **Unacceptable** (inadequate details and conduct, range-finding only). No worksheet. (Gee, 9/25/03)

\*\* 50820-005 125448 "91-Day dermal toxicity study in rats with MBT, final report." (Siglin, J. C., Springborn Laboratories, Inc., OH, SLS Study No. 3248.1, December 12, 1991) Ten Sprague-Dawley rats per sex per group were exposed to 2-mercaptobenzothiazole (lot N9H 211, 98.22%) at 0 (PEG 400), 200, 1000 or 2000 mg/kg/day, 6 hours per day, 5 days/week, for 13 weeks, by dermal application to clipped skin. The test mixtures were applied in 6.0 ml/kg to approximately 10 % of the body surface. The site was covered with gauze and an overwrap secured with tape. After the 6 hours, the wrap was removed and the area wiped with a moistened gauze. The low and mid doses were soluble in the PEG but at the high dose (333.33 mg/ml stock), a creamy suspension was formed. Dose selection was based on a range-finding study. There were no treatment-related effects on body weight, food consumption, or ophthalmology. There were occasional statistically significant changes in hematology or clinical chemistry but all were stated to be within the normal range. The relative liver weights for females at the mid and high doses were significantly increased, but not in males. There was no effect on skin at the sight of application and no other histological findings related to exposure. NOEL = 200 mg/kg/day based on the increased relative liver weight in females, without pathology. **Acceptable with no adverse effect.** (Gee, 10/8/03).

## CHRONIC TOXICITY, DOG

Data gap, no study on file.

## ONCOGENICITY, RAT

**No record number.** "Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)." (Dieter, M. P., Physiological Research Laboratories, Minneapolis, Minnesota, NTP TR 332, NIH Publication No. 88-2588, May 1988). 2-Mercaptobenzothiazole (lots V10479 and 39-7-D, purities of 96 and 97%) was given by gavage to 50 F344/N rats per sex per dose. Doses were 0 (corn oil), 375 or 750 mg/kg/day for males and 0, 188 or 375 mg/kg/day for females in a volume of 5 ml/kg, given 5 days per week for 103 weeks. Dose selection was based on a 13-week study. The text stated that animals were lethargic after dosing (no data). Survival at both doses in males was significantly lower, beginning week 83, compared with controls being 22/50 (375 mg/kg) and 20/50 (750 mg/kg) compared with 42/50 in controls. Survival of all groups of females was comparable. Body weights were not affected. In males, there was a significant increase in leukemia and pancreatic acinar cell adenomas at 375 mg/kg (not at 750 mg/kg), adrenal gland pheochromocytomas (both doses), preputial gland adenomas/carcinomas (both doses). In females, adrenal pheochromocytomas and pituitary gland adenomas showed a positive trend. The conclusion of the NTP review panel was "some evidence" for an oncogenic effect in both sexes. The primary non-neoplastic target organ was the forestomach with increases in ulcers, epithelial hyperplasia, hyperkeratosis and inflammation, with a greater response in males, often being statistically significant in pairwise comparison and increasing with dose. The text stated that the severity of nephropathy increased in males at both doses compared with controls but no data were provided. Unacceptable (two doses only, missing individual data, no blood smears, no organ weights). Not upgradeable. **Possible adverse effect** for oncogenic potential. (Gee, 9/26/03)

## ONCOGENICITY, MOUSE

Subchronic mouse

No record number or volume number. "Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)." (Dieter, M. P., Physiological Research Laboratories, Minneapolis, Minnesota, NTP TR 332, NIH Publication No. 88-2588, May 1988). 2-Mercaptobenzothiazole (lot V10479, purity of 96%) was given by oral gavage to B6C3F<sub>1</sub> mice, 10/sex/group, at doses of 0 (corn oil), 94, 188, 375, 750 or 1500 mg/kg/day, 5 days per week for 13 weeks. Mice were housed 5/cage and observed twice daily and weighed weekly. Necropsy was performed on all animals with a histology exam for selected animals (no details). At 1500 mg/kg/day, 5/10 males and 7/10 females died with 2 being related to gavage error. Body weights were not significantly affected. Clonic seizures, lacrimation and salivation were seen at 750 and 1500 mg/kg/day (no data). In addition, lethargy and rough coats were seen in the 375 and 750 mg/kg/day groups (no data). No gross or microscopic pathologic effects were noted. The relative weights of liver to body weight were higher in all dose groups, both sexes, with statistical significance at 1500 mg/kg/day for survivors. Based on mortality at 1500 mg/kg/day, a high dose of 750 mg/kg was selected for the 2-year study. No worksheet. **Unacceptable** (inadequate details and conduct, purpose was range-finding only). (Gee, 9/26/03)

**No record number.** " Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)." (Dieter, M. P., Physiological Research Laboratories, Minneapolis, Minnesota, NTP TR 332, NIH Publication No. 88-2588, May 1988). 2-Mercaptobenzothiazole (lots V10479 and 39-7-D, purities of 96 and 97%) was given by gavage to 50 mice per sex at 0 (corn oil), 375 or 750 mg/kg/day for 5 days per week for 103 weeks. Body weights of male mice were lower than controls at both doses through week 64. Females were within 6% of controls at the high dose and comparable for the low dose. Survival of female mice at the high dose was significantly lower than controls (22/50 versus 35/50 in controls,  $p = 0.005$ ). The incidence of hepatocellular adenoma or carcinoma combined in females at the low dose was statistically significantly increased (12/49 versus 4/50 in controls) but the incidence at the high dose was comparable (4/50, all adenomas). The incidences in males were 16/49, 21/50 and 14/50 with increasing dose. There were negative trends in females for pituitary adenoma or carcinoma combined and for malignant lymphoma. The conclusion of the NTP Panel was that there was **"equivalent" evidence for oncogenicity in female mice** and **"no" evidence in males.** **Unacceptable** (two doses, incomplete reporting). Not upgradeable. (Gee, 9/29/03)

#### REPRODUCTION, RAT

**\*\* 50820-004 123840** "Two Generation Reproduction Study in Rats with Mercaptobenzothiazole." (Springborn Life Sciences, Inc., Spencerville, OH., SLS Study # 3205.5, 7 December 1990). Twenty-eight Sprague Dawley Crl:CD<sup>®</sup>COBS<sup>®</sup>BR<sup>®</sup> rats per sex per group received 2-mercaptobenzothiazole (98.2% purity, lot N8F-228) in the diet at 0 (basal diet), 2500, 8750, and 15,000 ppm through 2 generations (1 litter per generation). Treatment began 70 days prior to mating for the F1 generation. Statistically significant mean pre-mating bodyweight reductions relative to controls were noted. For F0 parents, 4% to 8% reductions for both sexes were seen at the mid and high dose levels. In F1s, bodyweight was lower for both sexes by 9 % to 13 % at the mid-dose level and by 11 % to 22 % at the high dose throughout the pre-mating period. Note that F1 bodyweight was lower at these dose levels at the beginning of the pre-mating period (study week 18), due to reduced F1a pup growth. Hepatocyte hypertrophy was seen in the F1 parental animals along with increased relative liver weight. Parental NOEL = 2,500 ppm. Litter numbers and size and reproductive indices are generally comparable across groups. Reproductive NOEL = 15,000 ppm. **Retarded pup growth at all treatment levels in both generations was noted.** Mean F1a pup weights at day 21 were 5 %, 12 %, and 22 % lower than controls at the low, mid, and high dose levels respectively; for F2a pups, the reductions were 9 %, 12 %, and 20 % respectively. Pup NOEL < 2,500 ppm. **Acceptable.** (H. Green and Gee, 10/6/03).

#### TERATOLOGY, RAT

**\*\* 50820-003 123839** "Teratology Study in Rats with Mercaptobenzothiazole." (Dean E. Rodwell, Springborn Life Sciences, Inc., Spencerville, OH, SLS Study # 3205.2, 1990). Twenty-six presumed pregnant Sprague-Dawley Crl:COBS<sup>®</sup>CD<sup>®</sup>BR<sup>®</sup>VAF<sup>®</sup> female rats received 2-mercaptobenzothiazole (98.1 %, lot N8F-228) by gavage at 0 (corn oil at 10 ml/kg), 300, 1200, and 1800 mg/kg/day on gestation days 6 through 15. Bodyweights for the high dose dams were slightly reduced (4 %) on gestation day 9 with a weight loss of 9 grams compared with a gain of 3

grams in controls. Food consumption (grams/animal/day) was significantly reduced (29 %) for days 6 through 9 at 1800 mg/kg/day. Post-dosing (length of time following dosing not stated) increased incidences of urine staining and salivation were noted at 1200 and 1800 mg/kg/day. There were no incidences in controls but 7/5 at 1200 and 4/4 at 1800 mg/kg/day for urine staining and 38/17 and 35/15 at 1200 and 1800 mg/kg/day for salivation. However, the total incidence/number of animals for urine stain was not as clear as the controls showed an incidence of 10/8 during the study. The incidences of dark material around the mouth and nose and yellow-colored material around the mouth were increased at the low (slight), mid, and high dose levels relative to controls. Overall, however, controls also showed a low incidence of dark material around the nose (2/2). Maternal NOEL = 300 mg/kg/day (salivation and urine staining following gavage dosing at 1200 and 1800 mg/kg and a body weight effect at 1800 mg/kg/day). There were no abortions or total litter losses. Fetal weights were comparable as were mean litter sizes. Post-implantation loss was increased ( $p < 0.05$ ) at the high dose. Developmental NOEL = 1200 mg/kg/day. There was no treatment-related increase in malformations/variations. **Acceptable.** (H. Green and Gee, 10/2/03).

## TERATOLOGY, RABBIT

Data gap, no study on file.

## GENE MUTATION

\*\*50820-002 123835 "Ames Salmonella/Microsome Plate Test on Mercaptobenzothiazole" (Edmund G. Godek, Pharmakon Research International, Inc., Waverly, PA. Study Number Ph 301-CMA-001-83, PH 301-CMA-001-83A, 3 February 1984). Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538 were exposed to mercaptobenzothiazole (lot #39-14B, 98.1% purity) at concentrations of 0 (DMSO), 3, 10, 100, and 300  $\mu\text{g}/\text{plate}$  for 48 to 72 hours in the presence and absence of rat liver activation, duplicate plates per concentration, by the plate incorporation method. A second assay was performed using strains TA98 and TA1538 in the presence of activation only at 0 (DMSO), 100, 250, 300, 450, and 600  $\mu\text{g}/\text{plate}$ , duplicate plates. No increase in reversion frequency. Acceptable with minor deficiencies. (H. Green and Gee, 9/29/03)

50820-002 123836 "CHO/HGPRT Mammalian Cell Forward Mutation Assay of 2-Mercaptobenzothiazole." (Edmund G. Godek, Pharmakon Research International, Inc., Waverly, PA., Study Number PH 314-CMA-001-83, 3 February 1984). Chinese hamster ovary cells (CHO-K1-BH4) were exposed in duplicate cultures to mercaptobenzothiazole (lot #39-14B, 98.1% purity) at concentrations of 0 (untreated), 0 (DMSO), 1, 5, 10, 30, and 50  $\mu\text{g}/\text{ml}$  without activation and 0 (untreated), 0 (DMSO), 10, 25, 75, 150, and 300  $\mu\text{g}/\text{ml}$  with activation (source not described) for 5 hours followed by 19 hours before subculturing. A slight precipitate formed at 300  $\mu\text{g}/\text{ml}$ . After 8 days for expression, the cultures were plated in 5 plates for cloning efficiency and 5 for selection for mutant frequency. No increase in the frequency of forward mutation at the hgpert locus was found. Unacceptable (no repeat assay to confirm the negative results and no justification for not performing a repeat). (H. Green and Gee, 9/30/03)

No record number. "Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)." (Dieter, M. P., NTP TR 332, NIH Publication No. 88-2588, May 1988). 2-Mercaptobenzothiazole (purity not stated) was tested with *Salmonella*

*typhimurium* strains TA100, TA98, TA1535 and TA1537 in two laboratories, EG&G Mason Research Institute and Case Western Reserve University. Dimethyl sulfoxide was the solvent control at both laboratories. EG&G: A single assay with triplicate plates per concentration was reported with TA100, TA1535 and TA1537 and three trials with TA98. Concentrations tested ranged from 3.3 to 1000 ug/plate without and with S9 (from male Sprague Dawley rat and male Syrian hamster livers). Slight toxicity was noted by a decrease in spontaneous revertants at 1000 ug/plate, except for TA98. The results with TA98 with activation were considered "equivocal" or "weakly positive" in the first two trials but negative in the third trial. Positive controls were functional. Case Western Reserve: Two trials, without and with S9 from male rat and hamster livers, using concentrations ranging from 10 to 10,000 ug/plate, triplicate plates per concentration. Toxicity was noted at the higher concentrations, especially at 1000 ug/plate and higher. Precipitates formed at 3333 and 10,000 ug/plate. Results were considered to be negative in all strains, both trials. Positive controls were functional. No worksheet. Summary data only, methods by citation, therefore unacceptable. The full report is needed. (Gee, 9/29/03).

**No record number.** " Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)." (Dieter, M. P., NTP TR 332, NIH Publication No. 88-2588, Litton Bionetics, Inc., May 1988). 2-Mercaptobenzothiazole (purity not stated) was tested with mouse L5178Y lymphoma cells for mutagenicity. There were two trials without activation and three trials with S9 prepared from Aroclor 1254-induced F344 rat liver. Concentrations were 0 (ethanol), and 30 to 150 ug/ml without activation and 1.25 to 20 ug/ml with activation. There were triplicate cultures per concentration with exposure for 4 hours followed by a 48 hour expression period. Cells were plated in soft agar with trifluorothymidine for mutant selection and in nonselective medium for cloning efficiency. Results were reported as the mean  $\pm$  standard error. Without S9, the results were negative with 120 and 150 ug/ml being "lethal". Methyl methanesulfonate was functional. With activation, a positive result was found at 15 ug/ml, trial one, at all concentrations (5, 6, 8, 10, 12 and 16 ug/ml) in trial 2 and at the three highest concentrations (12, 16 and 20 ug/ml) in trial 3. Methylcholanthrene was functional in all three trials with activation. A positive response was defined as a relative mutant fraction of 1.6 or greater compared with controls. Unacceptable (summary data only, protocol primarily by citation). The full report is needed. **Possible adverse effect.** No worksheet. (Gee, 9/29/03).

## CHROMOSOME EFFECTS

\*\* 50820-002 123837 "Genetic Toxicology Micronucleus Test (MNT) of 2-Mercaptobenzothiazole with Addendum." (Ruth M. Sorg and Juan R. SanSebastian, Pharmakon Research International, Inc., Waverly, PA., Study Number PH 309A-CMA-001-83, 3 February 1984 and 8 June 1990 (Addendum)). Four CD-1 mice per sex per group received 2-mercaptobenzothiazole by intraperitoneal injection at 300 mg/kg once or twice (24-hour interval between doses). The dose was selected from a preliminary study using doses of 16.6 to 1666.6 mg/kg. All animals at 1666.6 died and 2/2 females died at 500 mg/kg after the first dose. Bone marrow sampling was 30 and 48 hours post-dosing for single dose groups and 48 and 72 hours after the first dose for animals given two doses. Negative control animals received 2 doses of corn oil 24 hours apart with sampling 48 hours after the initial dose. Positive control was triethylenemelamine. Clinical signs were seen after the first dose of 300 mg/kg but no deaths occurred. For each animal, 1000 polychromatic erythrocytes were examined for micronuclei, the NCE/PCE ratio determined and the micronuclei in normochromatic erythrocytes reported in the addendum. No increase in the number of micronuclei per 1000 polychromatic erythrocytes was indicated. Acceptable. (H. Green and Gee, 9/30/03).

**No record number.** " Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)." (Dieter, M. P., NTP TR 332, NIH Publication No. 88-2588, Litton Bionetics, Inc., May 1988). 2-Mercaptobenzothiazole (purity not stated) was tested with Chinese hamster ovary cells for sister chromatid exchange induction. Exposure without S9 was for approximately 26 or 33 hours and with Aroclor 1254-induced male Sprague Dawley rat liver activation, for 2 hours followed by an additional 24 or 34 hours. Due to cell cycle delay, incubation was increased to 33 or 36 hours for cells in the second metaphase. Concentrations without activation were 0 (DMSO), 12.5, 14.9, 20.1 and 24.8 ug/ml, single trial. With activation, in trial 1, concentrations were 0, 99.2, 247.5, 501.5 and 750 ug/ml. In trial 2 with activation, concentrations used were 351.6, 401.6, 445.3 and 502.3. BrdU was added to the medium to distinguish the chromatids. Cells were collected by mitotic shake-off and fixed and stained. Fifty cells per concentration were scored for SCEs. The relative SCEs/cell as percent of controls was reported. The results without activation were negative, being 94, 103 and 114 compared with vehicle control. The positive control, mitomycin C, was functional. With activation, the relative percent of sister chromatid exchanges increased with treatment, being 112, 113 and 135% in trial 1 and 123, 137 and 130 in trial 2, compared with the DMSO vehicle control. The positive control, cyclophosphamide, was functional. **Possible adverse effect.** Unacceptable (summary protocol and data only, not the full report.) Possibly upgradeable with the full study report. No worksheet. (Gee, 9/29/03).

**No record number.** " Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F<sub>1</sub> mice (gavage studies)." (Dieter, M. P., NTP TR 332, NIH Publication No. 88-2588, Litton Bionetics, Inc., May 1988). 2-Mercaptobenzothiazole (purity not stated) was tested with Chinese hamster ovary cells for chromosomal aberrations with and without S9. Without activation, cells were incubated for 8-10 hours with the test article at 0 (DMSO), 10, 14.9, 19.9 or 30.1 ug/ml followed by an additional 2-3 hours before harvesting cells in the first metaphase. With activation, there were two trials. Trial 1 used 352, 401, 451 or 500 ug/ml and trial 2 used 374, 399, 425 and 450 ug/ml. The percent of cells with aberrations was the same as control without activation. With activation, the percent of cells increased with exposure: Trial 1, control was 1%, treated values were 9, 9 and 16 with increasing concentration through 451 (no cells were scored at 500 ug/ml). Trial 2: 2% in controls with 24, 28 and 28% with increasing concentration with no cells scored at 450 ug/ml. Positive controls were functional. The types of aberrations were not described. **Possible adverse effect.** One page summary - the full report is needed. No worksheet. (Gee, 9/29/03).

**No record number.** "Chromosome aberration and sister chromatid exchange test results with 42 chemicals." (Anderson, B. E., E. Zeiger, M. D. Shelby, M. A. Resnick, D. K. Gulati, J. L. Ivett and K. S. Love-day, multiple laboratories, publ. in *Environmental and Molecular Mutagenesis* 16 (18): 55 - 137 (1990)) Summary of results including sister chromatid exchange and chromosomal aberration assays with 2-mercaptobenzothiazole. Some of the results appear to be the same as in the NTP TR 332 report above from Litton Bionetics with positive findings, especially with activation. No worksheet. (Gee, 11/19/03)

## DNA DAMAGE

50820-002 123838 "Unscheduled DNA Synthesis in Rat Primary Hepatocytes." (Roger D. Curren, Microbiological Associates, Inc., Rockville, MD., Study number T9190.380, 4 June 1990). Primary hepatocytes from male Fischer F344 rats were exposed in triplicate cultures

to 2-mercaptobenzothiazole (98.0 % purity, lot N9H211) at 0 (DMSO), 0 (WME, plating medium), 0.5, 1.5, 5.0, 15, 50, 100, and 150 µg/ml for 18 to 20 hours. Concentrations of 100 and 150 µg/ml were too toxic to evaluate. Toxicity after treatment was determined using the release of lactic acid dehydrogenase as well as morphology. No increase in unscheduled DNA synthesis under test conditions. The positive control was functional. Unacceptable (control cell viability during the study not included, summary data only rather than cytoplasmic and nuclear counts as well as net counts). Possibly upgradeable. (H. Green and Gee, 9/30/03).

## NEUROTOXICITY

Not required at this time.