

SOME INDUSTRIAL CHEMICALS

VOLUME 115

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of Carcinogenic Risks to Humans, which met in Lyon, 2–9 February 2016

LYON, FRANCE - 2018

IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS

2-MERCAPTOBENZOTHAZOLE

1. Exposure Data

1.1 Identification of the agent

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 149-30-4

Chem. Abstr. Serv. Name:

2-Mercaptobenzothiazole

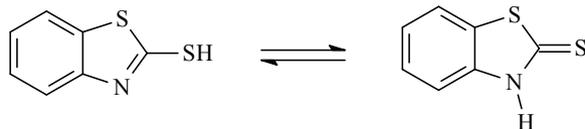
IUPAC Systematic Name:

3H-1,3-Benzothiazole-2-thione

Synonyms: Benzothiazole-2-thiol; 1,3-benzothiazole-2-thiol; 2-benzothiazolethiol; 3H-benzothiazole-2-thione; 2-sulfanylbenzothiazole

Acronyms: MBT; 2-MBT.

1.1.2 Structure and molecular formula, and relative molecular mass



(tautomers in crystals and aqueous solutions)

Molecular formula: $C_7H_5NS_2$

Relative molecular mass: 167.25

1.1.3 Physical and chemical properties of the pure substance

Description: Yellowish crystals or powder with a characteristic sulfurous odour ([IFA, 2015](#))

Melting point: 180–182 °C ([HSDB, 2015](#))

Density (at 20 °C): 1.42 g/cm³ ([HSDB, 2015](#))

Octanol/water partition coefficient: log K_{ow} , 2.41 ([HSDB, 2015](#))

Water solubility: Moderately soluble (100–1000 mg/L) ([ECHA, 2015](#))

Dissociation constant: pK_a 7.0 at 20 °C ([HSDB, 2015](#))

Volatility: Vapour pressure, 2.25×10^{-8} mm Hg at 20 °C ([HSDB, 2015](#))

Flash point: 243 °C ([GESTIS, 2015](#))

Conversion factor: 1 ppm = 6.83 mg/m³ ([HSDB, 2015](#)).

1.2 Production and use

1.2.1 Production

(a) Production process

2-Mercaptobenzothiazole is produced by reacting aniline, carbon disulfide, and sulfur at high temperature and pressure; the product is then purified by dissolution in a base to remove the dissolved organics. Re-precipitation is achieved by the addition of acid ([Kirk-Othmer, 1982](#); [NTP, 1988](#)).

(b) Production volume

2-Mercaptobenzothiazole is listed as a chemical with high production volume by the Organisation for Economic Co-operation and Development (OECD, 2004) and in the USA (Federal Register, 2000; HSDB, 2015).

In 2006, the inventory-aggregated national production volume for 2-mercaptobenzothiazole in the USA was between 10 and < 50 million pounds [~4536 to < 22 680 tonnes]. The United States Environmental Protection Agency (EPA) noted that 500 000–1 000 000 pounds/year [~227–454 tonnes/year] of 2-mercaptobenzothiazole were produced, imported, and used in the USA in 2012 (EPA, 2012). In 2012, three facilities in three states were listed as manufacturing 2-mercaptobenzothiazole in the USA (HSDB, 2015).

2-Mercaptobenzothiazole is registered with the European Chemicals Agency, and production was stated to be 1000–10 000 tonnes per year from three manufacturers in three countries, one each in Belgium, Spain, and the United Kingdom (ECHA, 2012).

A commercial website identified a larger number of suppliers: 225 in China, 13 in the USA, five in India, two in Hong Kong Special Administrative Region, and one each in Canada, France, Germany, Japan, the Russian Federation, and Turkey (GuideChem, 2015).

1.2.2 Use

2-Mercaptobenzothiazole is principally used as a reactant in the manufacture of rubber products, but is also used as a corrosion inhibitor in oils, greases and cooling fluids. It is added to polyether polymers as a stabilizer to resist damage by air and ozone, and is a component approved in the USA in some skin medications for dogs (HSDB, 2015).

2-Mercaptobenzothiazole is also used as an intermediate in the production of pesticides such as 2-(thiocyanomethylthio)benzothiazole

(Azam & Suresh, 2012), and sodium and zinc salts of 2-mercaptobenzothiazole are approved for use as pesticides by the EPA (1994).

1.3 Measurement and analysis

Several analytical methods are available for the determination of 2-mercaptobenzothiazole in environmental samples (e.g. air, water, and food), in rubber products (e.g. disposable medical gloves), in products that come into contact with rubber materials (e.g. medical drug solutions or industrial coolant solutions), and in the urine of exposed persons (Table 1.1). Generally, the use of stable isotope-labelled surrogate standards is recommended for the specific analysis of 2-mercaptobenzothiazole (Wick et al., 2010). A single method has been described for the determination of 2-mercaptobenzothiazole in dietary products (Barnes et al., 2003).

1.4 Occurrence and exposure

Due to its use as an accelerant in rubber vulcanization, 2-mercaptobenzothiazole can be found as a contaminant in rubber products. Sensitization to 2-mercaptobenzothiazole is common in occupational and non-occupational settings and can be used as an indicator of exposure (HSDB, 2015).

1.4.1 Natural occurrence

2-Mercaptobenzothiazole is not known to occur in nature.

1.4.2 Environmental occurrence

(a) Air

Urban particulate matter was sampled in a street in Stockholm, Sweden, using a device made in-house; average concentrations of 2-mercaptobenzothiazole were 64 pg/m³ in airborne particulate matter, and 591 pg/m³ in total suspended particulate matter, and were thought to derive from tyre wear (Avagyan et al., 2014).

Table 1.1 Selected methods of analysis for 2-mercaptobenzothiazole

| Sample matrix | Sample preparation | Assay method | Limit of detection | Reference |
|---|--|----------------|-------------------------|--|
| <i>Air</i> | | | | |
| Workplace air | Collection on quartz fibre filters; stabilization by covering with double-distilled water; desorption using an ultrasonic bath; filtration of the sample Sampling recommendation: 2 h at 1 L/min (120 L) | CE/DAD | 0.2 mg/m ^{3a} | Breuer et al. (2002) |
| <i>Water</i> | | | | |
| Municipal and industrial wastewater | Extraction using methylene chloride at pH 6–8; drying and concentrating the sample; change solvent to methanol; if necessary: silica gel column clean-up | HPLC/UV | 1.7 µg/L | EPA (1993) |
| Treated and raw wastewater | Direct injection of the (diluted) effluent samples | HPLC/ESI-MS/MS | 0.2 µg/L | Reemtsma (2000) |
| Treated wastewater and raw municipal wastewater | SPE using a co-polymeric sorbent (divinylbenzene, <i>N</i> -vinylpyrrolidone); elution with methanol/acetone; addition of the internal standard; concentration of the eluent | HPLC/ESI-MS | 0.05 µg/L 0.12 µg/L | Kloepfer et al. (2004a) |
| Cooling water (spiked) | Direct analysis of the undiluted samples at pH 8 (buffered) | SWV | 0.8 mg/L | Parham et al. (2008) |
| Cooling water (spiked) | SPE using a cartridge loaded with copper oxide nanoparticles at pH 5–8; washing the sorbent with 0.5 M sodium thiosulfate; desorption of the cartridge using methanol | HPLC/UV | 1.9 µg/L | Parham & Khoshnam (2013) |
| Cooling water and drinking-water (spiked) | Addition of gold nanoparticle solution and citrate buffer (pH 6) | RRS, SFP | 1.0 µg/L | Parham et al. (2015) |
| <i>Food</i> | | | | |
| Dietary products | Milk, yoghurt, infant formula: addition of an internal standard; protein precipitation by the addition of acetonitrile; sample filtration All other foodstuffs: addition of an internal standard, acetic acid and acetonitrile; sonication of the sample followed by centrifugation and filtering | HPLC/APCI-MS | 8–43 µg/kg ^b | Barnes et al. (2003) |
| <i>Products</i> | | | | |
| Coolant formulations | Direct analysis of the undiluted samples | HPLC/UV | 0.02% | Schmitt & Muzher (1981) |
| Injectable solutions | Mixing with 1 M hydrochloric acid; extraction with chloroform; evaporation to dryness and reconstitution in acetonitrile | HPLC/UV | NA | Reepmeyer & Juhl (1983) |
| Protective gloves | Extraction using acetone; evaporation to dryness and reconstitution in acetonitrile; filtration of the sample | HPLC/DAD | 1 mg/L | Bergendorff et al. (2006) |

Table 1.1 (continued)

| Sample matrix | Sample preparation | Assay method | Limit of detection | Reference |
|--|--|----------------|--------------------|--|
| <i>Urine</i> | | | | |
| Experimental animals | Acidic hydrolysis using 5 M sulfuric acid; incubation at room temperature; SPE using C ₁₈ cartridges; elution with ethyl acetate; evaporation to dryness and reconstitution in ethanol | GC/MS | 20 µg/L | Manninen et al. (1996) |
| Exposed workers and non-exposed controls | Homogenization and addition of ammonium acetate buffer (pH 6.5), deuterated internal standard (MBT-d ₄) and β-glucuronidase/arylsulfatase; homogenization of the samples, incubation overnight at 37 °C and centrifugation | HPLC/ESI-MS/MS | 0.4 µg/L | Gries et al. (2015) |

^a The analysis is considered to be semi-quantitative. The coefficient of variation of the calibration is 1.8%, therefore the analytical procedure itself is precise; however, due to the instability of 2-mercaptobenzothiazole on the filter, large overall variation can occur (up to 16% depending on the concentration)

^b Depending on the food

APCI, atmospheric pressure chemical ionization; CE, capillary electrophoresis; DAD, diode array detection; ESI, electrospray ionization; GC, gas chromatography; HPLC, high-performance liquid chromatography; MBT, 2-mercaptobenzothiazole; MS, mass spectrometry; MS/MS, tandem mass spectrometry; NA, not available; RRS, resonance Raleigh scattering; SFP, spectrofluorometry; SPE, solid-phase extraction; SWV, square wave voltammetry; UV, ultraviolet detection

(b) *Water*

Effluent from a waste dump was analysed for 2-mercaptobenzothiazole by liquid chromatography in a study aimed at developing analytical methods; the concentration of 2-mercaptobenzothiazole was estimated at 30 µg/L in the sample tested (Cox, 1976).

A study of municipal wastewater in Germany found 2-mercaptobenzothiazole at a concentration of up to 0.19 µg/L (Kloepfer et al., 2004b). In a comprehensive survey of wastewater from 4000 industrial and publicly owned treatment works sponsored by the Effluent Guidelines Division of the EPA, 2-mercaptobenzothiazole was identified in one discharge each from a rubber-processing and pesticide-manufacturing industry at a concentration of 1.27 ppm [8.67 µg/L] and 0.86 ppm [5.87 µg/L], respectively (Shackelford et al., 1983). The mean concentration of 2-mercaptobenzothiazole in the effluent from a paper mill was 0.025 ppm [0.17 µg/L] (Keith, 1976), and a concentration of 30 µg/L was found in the wastewater from a tyre-manufacturing plant (Jungclaus et al., 1976). 2-Mercaptobenzothiazole has been detected in tannery wastewater at concentrations ranging from 420 to 840 µg/L (Rodríguez et al., 2004), and in trace amounts in natural surface-water samples as a degradation product of the wood preservative 2-(thiocyanomethylthio)benzothiazole, which leaked from an upstream sawmill (Khoroshko et al., 2005).

(c) *Products*

(i) *Medical devices*

An investigation of adverse reactions to an excretory urography contrast agent detected 2-mercaptobenzothiazole at concentrations of up to 3.3 µg/mL. At this concentration, a dose of the contrast agent of 100 mL would contain 0.33 mg of 2-mercaptobenzothiazole (Hamilton, 1987).

Leaching of 2-mercaptobenzothiazole into drug preparations of several constituents of elastomeric closures was assessed. In syringe cartridges, concentrations of 2-mercaptobenzothiazole ranged from 8.3 to 13.8 µg/mL (Airaud et al., 1990).

An investigation of instability of a therapeutic protein for infusion revealed that 2-mercaptobenzothiazole and its zinc salt leached from the stopper used for the infusion bags (100 mL) (Chang et al., 2010).

(ii) *Consumer products*

A survey of 19 rubber gloves found that two contained 2-mercaptobenzothiazole (5–8 µg/g) (Bergendorff et al., 2006).

In 2001, a retail market survey of 19 samples of baby bottle teats and soothers was performed in the Netherlands. The migration of 2-mercaptobenzothiazole was detected in only one natural rubber sample, and was considerably lower than the limit of 0.3 mg/teat (Bouma et al., 2003).

In the United Kingdom, in 2000, 2-mercaptobenzothiazole was not detected in 236 retail samples of food that may have been in contact with rubber material during their fabrication, transport, or storage (Barnes et al., 2003).

1.4.3 Occupational exposure

2-Mercaptobenzothiazole has been detected in the urine samples of four workers employed at a plant producing 2-mercaptobenzothiazole, one worker from the administration department of the plant, and only one out of forty persons not knowingly exposed to 2-mercaptobenzothiazole (Gries et al., 2015). Mean concentrations of 2-mercaptobenzothiazole in the four exposed workers were 3958 µg/L after enzymatic hydrolysis of the urine sample during sample preparation; without hydrolysis, the concentration determined was only 69 µg/L. The results showed that most 2-mercaptobenzothiazole in the urine was excreted in conjugated forms (e.g.

2-mercaptobenzothiazole glucuronide) rather than in its unchanged form. Using this method (with hydrolysis), 2-mercaptobenzothiazole was detected in only one (11 µg/L) out of the 40 samples of urine collected from non-exposed individuals. The person from the administration department excreted 2-mercaptobenzothiazole at 2.5 µg/L and was thus within the range for non-exposed individuals.

The data from all employed patients (age range, 16–68 years; $n = 14\ 234$) patch-tested between 2003 and 2013 in the German Information Network of Departments of Dermatology, and diagnosed as having occupationally acquired contact dermatitis were analysed. The control group comprised all other patients ($n = 31\ 706$) within the same time frame who tested negative for occupationally acquired allergic contact dermatitis. The prevalence ratio (indicating risk) was significantly increased for 2-mercaptobenzothiazole (prevalence ratio, 3.88; 95% confidence interval [CI], 3.09–4.89) ([Bauer et al., 2015](#)).

A series of 23 patients with allergic contact dermatitis (some with disseminated dermatitis) due to rubber accelerators in rubber gloves treated during a 2-year period was described. Sixteen were health-care workers from a single institution whose dermatitis was temporally related to the switch to latex-safe gloves. Each had positive patch-test reactions to one or more rubber accelerators, including 2-mercaptobenzothiazole. Chemical analysis identified 2-mercaptobenzothiazole in four out of six glove samples ([Cao et al., 2010](#)).

A retrospective analysis of data from the Information Network of Departments of Dermatology in 2002–10 found that, of 93 615 patients who were patch tested, 3448 had occupational dermatitis and were tested because of a suspected glove allergy. Of all the occupational dermatitis patients, 3% were sensitized to 2-mercaptobenzothiazole and/or its derivatives ([Geier et al., 2012](#)).

Standard patch test results of employed persons with an initial report of an occupational skin disease were analysed within 24 occupational groups. Among the occupationally relevant sensitizers, mercapto-mix/mercapto-benzothiazole contributed to 35% of the positive results ([Dickel et al., 2002](#)).

1.4.4 Exposure of the general population

Case reports that included a patch test confirmed that contact with 2-mercaptobenzothiazole was from a foley catheter ([Ancona et al., 1985](#)), a rubber earplug ([Deguchi & Tagami, 1996](#)), safety shoes ([Foussereau et al., 1986](#)), rubber gloves ([Geier et al., 2012](#)), a condom catheter ([Harmon et al., 1995](#)), and a bikini with rubberized elastic ([Jung et al., 2006](#)).

A total of 155 cases with footwear dermatitis were evaluated from July 2005 to June 2006 from detailed histories, clinical examinations, and patch testing. Contributory allergens included 2-mercaptobenzothiazole (12.9%; $n = 20$) ([Chowdhuri & Ghosh, 2007](#)).

In a study of dermatitis among athletes, 43 young adults (31 men and 12 women) with eczematous skin lesions suggesting allergic contact dermatitis were patch-tested; 21% tested positive for 2-mercaptobenzothiazole ([Ventura et al., 2001](#)).

Investigators in Spain used gas chromatography–mass spectrometry to analyse the 2-mercaptobenzothiazole content of samples of crumb rubber from urban playgrounds and from rubber pavers. Ten of the 21 samples from playgrounds contained quantifiable 2-mercaptobenzothiazole (mean, 195 µg/g; median, 185 µg/g; maximum, 398 µg/g). No 2-mercaptobenzothiazole was detected in the nine samples from rubber pavers analysed ([Llompart et al., 2013](#)).

1.4.5 Exposure assessment in epidemiological studies

[Strauss et al. \(1993\)](#) studied a production facility in West Virginia, USA, where 2-mercaptobenzothiazole had been produced since 1934. A former plant industrial hygienist developed annual airborne exposure estimates throughout the study period for all hourly production jobs, using sampling data available from 1977 to 1989, historical company documents, and interviews with knowledgeable retirees for the period before 1977. Jobs with potential exposure to 2-mercaptobenzothiazole were assigned to four exposure categories: very low ($>0-0.5 \text{ mg/m}^3$), low ($>0.5-2.0 \text{ mg/m}^3$), medium ($>2.0-5.0 \text{ mg/m}^3$) and high ($>5.0-20.0 \text{ mg/m}^3$). Jobs in these categories were not named. A cumulative exposure index for each job was calculated by multiplying the midpoint of each exposure category by duration in a 2-mercaptobenzothiazole-exposed job. Three categories of cumulative exposure to 2-mercaptobenzothiazole were calculated: $< 2 \text{ mg/m}^3\text{-year}$ (46% of the cohort), $2-7 \text{ mg/m}^3\text{-year}$ (32% of the cohort), and $8-129 \text{ mg/m}^3\text{-year}$ (22% of the cohort). No description of the processes was included in the report, therefore no information on exposure characteristics by process could be derived. [Collins et al. \(1999\)](#) extended the follow-up of this cohort and noted that, in 1943–54, average exposures generally exceeded 2 mg/m^3 . Again, no information on the processes was provided.

A mortality study was conducted among employees at a plant in Wales, United Kingdom, that had manufactured 2-mercaptobenzothiazole since 1932 and other chemicals, including *ortho*-toluidine, aniline, phenyl- β -naphthylamine, and polymerized 2,2,4-trimethyl-1,2-dihydroquinoline. A former occupational hygienist from the plant provided assessments of 8-hour time-weighted average (TWA) exposures to both 2-mercaptobenzothiazole and its derivatives over a range of years and for each job and department

title. Various jobs entailed either zero exposure, very low ($0-1 \text{ mg/m}^3$), low ($1-2.5 \text{ mg/m}^3$), medium ($2.5-6 \text{ mg/m}^3$) or high ($6-20 \text{ mg/m}^3$) exposure. Estimates were made on the basis of monitoring data from 1977 onwards, a review of process manuals and other company records for earlier years, and discussions with long-serving employees. Annual exposure estimate were adjusted by a “year fraction” factor per job, to take into account the duration of exposure for a working year. Cumulative exposure strata were reported as none, $0.01-21.24 \text{ mg/m}^3\text{-year}$, $21.25-63.74 \text{ mg/m}^3\text{-year}$, and $\geq 63.75 \text{ mg/m}^3\text{-year}$. No description of the processes was supplied and no exposures by process or distribution of workers by exposure strata were reported ([Sorahan & Pope, 1993](#)). A second report on this cohort provided further details of the matrix of exposure levels by job title and year. The highest exposures were 11.7 mg/m^3 for day pack and pellet operators, and 8.5 mg/m^3 for bag flake operators and daymen. The same cumulative exposure strata were reported ([Sorahan et al., 2000](#)). A third update ([Sorahan, 2008](#)) and a fourth update ([Sorahan, 2009](#)) of this cohort used the same exposure assessment. [The Working Group noted that exposure to 2-mercaptobenzothiazole dust would be associated with jobs identified within the compounding area or described as batch preparation. Downstream, skin contact with expressed 2-mercaptobenzothiazole and absorption would be higher in jobs before curing (green rubber), such as milling, calendaring, and tyre building, although there may still be skin absorption from cured rubber.]

1.5 Regulations and guidelines

The legal occupational exposure in Germany for 2-mercaptobenzothiazole is 4 mg/m^3 inhalable dust. No other permissible limits were found ([GESTIS, 2015](#)).

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

designation of 2-mercaptobenzothiazole is H317, “may cause an allergic skin reaction” and H410 “very toxic to aquatic life with long-lasting effects” (ECHA, 2015).

2. Cancer in Humans

See [Table 2.1](#)

A series of studies of workers at a chemical production plant in north Wales, United Kingdom, provided most of the pertinent evidence pertaining to associations between occupational exposure to 2-mercaptobenzothiazole and cancer (Sorahan & Pope, 1993; Sorahan et al., 2000; Sorahan, 2008, 2009). Some workers in the plant were also exposed to other chemicals (aniline, phenyl- β -naphthylamine, *ortho*-toluidine, and polymerized 2,2,4-trimethyl-1,2-dihydroquinoline) (Sorahan et al., 2000).

Within a cohort of 2160 male production workers employed for at least 6 months and with some employment during 1955–84, 363 were exposed to 2-mercaptobenzothiazole, 94 were exposed to phenyl- β -naphthylamine, 53 were exposed to *ortho*-toluidine, and 442 were exposed to aniline, but overlaps among the exposed groups were not specified (Sorahan, 2008). Sorahan (2008) focused on morbidity and mortality from cancer of the urinary bladder in the cohort exposed to 2-mercaptobenzothiazole and found an excess in mortality (8 deaths; standardized mortality ratio [SMR], 3.74; 95% CI, 1.62–7.37) and incidence (12 cases; standardized relative risk [SRR], 2.53; 95% CI, 1.31–4.41) compared with national rates (population of England and Wales). In an internal multivariate analysis of incident bladder cancer using the full cohort and adjusting for age, calendar period, and duration of employment with exposure to *ortho*-toluidine, aniline, and phenyl- β -naphthylamine, a positive non-significant trend

($P = 0.16$) was found with cumulative exposure to 2-mercaptobenzothiazole (0.01–21.24 mg/m³-year: 6 cases; relative risk [RR], 0.97; 95% CI, 0.38–2.43; 21.25–63.74 mg/m³-year: 6 cases; RR, 1.70; 95% CI, 0.65–4.41; ≥ 63.75 mg/m³-year: 3 cases; RR, 2.12; 95% CI, 0.64–7.06). The 15 cases in the three exposed groups included three with benign or in-situ tumours.

A subsequent report that presented data on the mortality from and incidence of cancers other than those of the urinary bladder among male workers exposed to 2-mercaptobenzothiazole relative to unexposed workers found excesses for cancers of the large intestine, lung and multiple myeloma (Sorahan, 2009). In the subcohort exposed to 2-mercaptobenzothiazole, there were eight deaths (SMR, 2.32; 95% CI, 1.00–4.57) from and nine diagnoses (SRR, 1.81; 95% CI, 0.83–3.44) of cancer of the large intestine, 27 deaths (SMR, 1.38; 95% CI, 0.91–2.01) from and 26 diagnoses (SRR, 1.52; 95% CI, 0.99–2.23) of lung cancer, and three deaths (SMR, 4.40; 95% CI, 0.91–12.87) from and four diagnoses (SRR, 4.65; 95% CI, 1.27–11.91) of multiple myeloma. In internal multivariate analyses of incidence in the full cohort that adjusted for the duration of employment with exposure to *ortho*-toluidine, aniline and phenyl- β -naphthylamine, significant trends of increased incidence with increased cumulative exposure to 2-mercaptobenzothiazole remained for cancer of the large intestine ($P < 0.001$) and multiple myeloma ($P = 0.019$). [The trend analysis for multiple myeloma was based on small numbers (4 exposed cases).]

Collins et al. (1999) studied a cohort of 1059 male chemical-production workers in Nitro, West Virginia, USA, exposed to 2-mercaptobenzothiazole and 4-aminobiphenyl (classified in IARC Group 1 as a cause of cancer of the urinary bladder) in an update of a report by Strauss et al. (1993). Among 511 2-mercaptobenzothiazole workers with no documented exposure to 4-aminobiphenyl, five deaths from urinary bladder cancer (SMR, 4.3; 95% CI, 1.4–10.0)

Table 2.1 Cohort studies of cancer and exposure to 2-mercaptobenzothiazole

| Reference, location, enrolment/ follow-up period | Population size, description; method of exposure assessment | Organ site | Exposure category or level | No. of exposed cases/ deaths | Risk estimate (95% CI) | Covariates controlled | Comments |
|--|--|----------------------|--|------------------------------|------------------------|-----------------------|---|
| Collins et al. (1999) Nitro, WV, USA 1955–77 | 1059 (600 with MBT exposure), white male production workers active for ≥ 1 day; JEM Social Security Administration, National Death Index, motor vehicle bureau, credit records | All cancers combined | Total MBT cohort | 63 | 1.0 (0.8–1.3) | NR | Strengths: extended follow-up Limitations: sampling data from 1977–89 only; no data on cigarette smoking |
| | | | Job involving MBT with 4-ABP | 23 | 2.0 (1.3–3.0) | | |
| | | | Job involving MBT without 4-ABP | 40 | 0.8 (0.5–1.0) | | |
| | | Lung | Total MBT cohort | 27 | 1.0 (0.7–1.5) | NR | |
| | | | Job involving MBT with 4-ABP | 11 | 2.4 (1.2–4.3) | | |
| | | | Job involving MBT without 4-ABP | 16 | 0.7 (0.4–1.2) | | |
| | | Prostate | Total MBT cohort | 4 | 0.9 (0.2–2.3) | NR | |
| | | | Job involving MBT without 4-ABP | 4 | 1.1 (0.3–2.9) | | |
| | | Urinary bladder | Total MBT cohort | 13 | 8.9 (4.7–15.2) | NR | |
| | | | Job involving MBT with 4-ABP | 8 | 27.1 (11.7–53.4) | | |
| | | | Job involving MBT without 4-ABP | 5 | 4.3 (1.4–10.0) | | |
| | | | Unexposed to MBT or 4-ABP | 1 | 1.2 (0.0–6.5) | | |
| | | | Cumulative exposure, < 2 mg/m ³ -year, no 4-ABP | 0 | 0.0 (0.0–13.8) | | |
| | | | Cumulative exposure, 2–7.9 mg/m ³ -year, no 4-ABP | 1 | 3.5 (0.1–19.5) | | |
| | | | Cumulative exposure, 8–129 mg/m ³ -year, no 4-ABP | 4 | 6.5 (1.8–16.6) | | |
| Trend test <i>P</i> -value: | | 0.04 | | | | | |

Table 2.1 (continued)

| Reference, location, enrolment/ follow-up period | Population size, description; method of exposure assessment | Organ site | Exposure category or level | No. of exposed cases/ deaths | Risk estimate (95% CI) | Covariates controlled | Comments |
|--|---|------------------------|---|------------------------------|------------------------|---|--|
| Sorahan (2008) North Wales, UK 1955–2005 | 2160 men, hourly staff working for ≥ 6 mo; 8-h TWA to MBT, MBT derivatives, by job and department: zero, very low (0–1 mg/m ³), low (1–2.5 mg/m ³), medium (2.5–6 mg/m ³), high (6–20 mg/m ³) 363 men exposed to MBT, 94 men exposed to PBN, 442 men exposed to aniline, 53 men exposed to <i>ortho</i> -toluidine) Office of National Statistics | Urinary bladder | 0 | 41 | 1.00 | Duration of employment in departments with exposure to PBN, aniline and <i>ortho</i> -toluidine Age, sex, and period Age, sex, and period | Trend analysis included benign or in-situ tumours. Strengths: long follow-up, little loss to follow-up Limitations: levels estimated based on monitoring data ≥ 1977, 266 workers in > 1 subcohort, 8 workers in all 4 subcohorts, cancer morbidity data only from 1971 to 2005 |
| | | | 0.01–21.24 mg/m ³ -year (RR) | 6 | 0.97 (0.38–2.43) | | |
| | | | 21.25–63.74 mg/m ³ -year (RR) | 6 | 1.70 (0.65–4.41) | | |
| | | | ≥ 63.75 mg/m ³ -year (RR) | 3 | 2.12 (0.64–7.06) | | |
| | | | Trend test <i>P</i> -value: 0.16 | | | | |
| SMR | 8 | 3.74 (1.62–7.37) | | | | | |
| | | SRR | 12 | 2.53 (1.31–4.41) | | | |
| Sorahan (2009) North Wales, UK 1955–2005 | 2160 men (363 in MBT subcohort), hourly staff working ≥ 6 mo and some employment 1955–84; 8-h TWA to MBT, MBT derivatives, by job and department: zero, very low (0.1–1 mg/m ³), low (1–2.5 mg/m ³), medium (2.5–6 mg/m ³) and high (6–20 mg/m ³) Office of National Statistics | Colon: large intestine | SMR | 8 | 2.32 (1.00–4.57) | Duration of employment in departments with exposure to PBN, aniline, and <i>ortho</i> -toluidine | Cases represent incidence and include death certificate notifications. Report focused on MBT and adjusted for other chemical exposures Strengths: long follow-up, little loss to follow-up Limitations: levels estimated based on monitoring data ≥ 1977, most workers exposed to > 1 chemical |
| | | | SRR | 9 | 1.81 (0.83–3.44) | | |
| | | | Cumulative exposure, 0 (RR) | 27 | 1.00 | | |
| | | | Cumulative exposure, 0.01–21.24 mg/m ³ -year (RR) | 3 | 1.24 (0.36–4.26) | | |
| | | | Cumulative exposure, 21.25–63.74 mg/m ³ -year (RR) | 6 | 4.76 (1.82–12.43) | | |

Table 2.1 (continued)

| Reference, location, enrolment/ follow-up period | Population size, description; method of exposure assessment | Organ site | Exposure category or level | No. of exposed cases/ deaths | Risk estimate (95% CI) | Covariates controlled | Comments |
|---|---|------------|---|------------------------------|------------------------|---|----------|
| Sorahan (2009) North Wales, UK 1955–2005 (cont.) | | Lung | Cumulative exposure, > 63.75 mg/m ³ -year (RR) | 3 | 4.69 (1.38–15.90) | Duration of employment in departments with exposure to PBN, aniline and <i>ortho</i> -toluidine | |
| | | | Trend test <i>P</i> -value: < 0.001 | | | | |
| | | | SMR | 27 | 1.38 (0.91–2.01) | | |
| | | | SRR | 26 | 1.52 (0.99–2.23) | | |
| | | | Cumulative exposure, 0 (RR) | 107 | 1.00 | | |
| | | | Cumulative exposure, 0.01–21.24 mg/m ³ -year (RR) | 21 | 2.17 (1.30–3.61) | | |
| | | | Cumulative exposure, 21.25–63.74 mg/m ³ -year (RR) | 4 | 0.65 (0.23–1.81) | | |
| | | | Cumulative exposure, ≥ 63.75 mg/m ³ -year (RR) | 4 | 1.44 (0.53–3.96) | | |
| Trend test <i>P</i> -value: 0.38 | | | | | | | |

Table 2.1 (continued)

| Reference, location, enrolment/ follow-up period | Population size, description; method of exposure assessment | Organ site | Exposure category or level | No. of exposed cases/ deaths | Risk estimate (95% CI) | Covariates controlled | Comments |
|---|---|----------------------|---|------------------------------|------------------------|---|----------|
| Sorahan (2009) North Wales, UK 1955–2005 (cont.) | | Multiple myeloma | SMR | 3 | 4.40 (0.91–12.87) | Duration of employment in departments with exposure to PBN, aniline and <i>ortho</i> -toluidine | |
| | | | SRR | 4 | 4.65 (1.27–11.91) | | |
| | | | Cumulative exposure, 0 (RR) | 2 | 1.00 | | |
| | | | Cumulative exposure, 0.01–21.24 mg/m ³ -year (RR) | 2 | 10.21 (1.27–81.7) | | |
| | | | Cumulative exposure, 21.25–63.74 mg/m ³ -year (RR) | 2 | 20.57 (2.58–164.00) | | |
| | | | Trend test <i>P</i> -value: 0.019 | | | | |
| | | All cancers combined | SMR | 76 | 1.41 (1.11–1.77) | NR | |
| | SRR | 97 | 1.48 (1.20–1.81) | | | | |

4-ABP, 4-aminobiphenyl; CI, confidence interval; JEM, job–exposure matrix; MBT, 2-mercaptobenzothiazole; mo, month; NR, not reported; PBN, phenyl- β -naphthylamine; RR, relative risk; SMR, standardized mortality ratio; SRR, standardized relative risk; TWA, time-weighted average

occurred. The standardized mortality ratios for bladder cancer in this cohort also showed a statistically significant increasing trend with increasing cumulative exposure to 2-mercaptobenzothiazole (P for trend = 0.04). No excess or trend was reported for lung cancer overall, or among workers exposed only to 2-mercaptobenzothiazole; however, the SMR for workers also exposed to 4-aminobiphenyl was elevated (SMR, 2.4; 95% CI, 1.2–4.3). No findings were presented for multiple myeloma or colon cancer in the cohort exposed to 2-mercaptobenzothiazole.

The use of 2-mercaptobenzothiazole was mentioned in studies conducted at another rubber chemical plant by the United States National Institute for Occupational Safety and Health (NIOSH), but results for urinary bladder cancer were only given for exposure to *ortho*-toluidine (NIOSH, 1989, 1992; Carreón et al., 2014).

3. Cancer in Experimental Animals

See [Table 3.1](#)

3.1 Mouse

Oral administration

Groups of 18 male and 18 female B6C3F₁ and C57BL/6 × AKR mice (age, 7 days) received 2-mercaptobenzothiazole [purity not reported; “commercial product” Captax] at a dose of 0 (control) or 100 mg/kg body weight (bw) in 0.5% gelatin daily by gavage for 3 weeks, followed immediately by continuous treatment with diets containing 2-mercaptobenzothiazole at a concentration of 0 (control) or 323 ppm for up to 18 months. [These dose rates were considered to be the maximal tolerated dose based on short-term studies of dose-related mortality.] Control mice were housed in the same room. At 18 months, mice were subjected to a post-mortem evaluation of the major thoracic and abdominal

organs and the thyroid, but the cranium was not dissected. Results were characterized as the incidence of hepatoma, pulmonary tumours, and lymphoma, and the total number of mice with tumours. Statistical analyses compared treated mice by sex and strain combination with five pooled negative-control groups using the Mantel-Haenszel procedure for the combined relative risk, using the weighted geometric mean with the ½ correction. Under the conditions of this study, administration of 2-mercaptobenzothiazole did not cause a significant increase in the incidence of tumours (Innes et al., 1969). [The limitations of this single-dose study were the small number of animals per group and the inadequate reporting of results, including the lack of information on survival, and the limited macroscopic and microscopic post-mortem evaluation. The Working Group considered this study to be inadequate for an evaluation of the carcinogenicity of 2-mercaptobenzothiazole.]

Groups of 50 male and 50 female B6C3F₁ mice (age, 8 weeks) were given 2-mercaptobenzothiazole (purity, 96.3%) at a dose of 0, 375, or 750 mg/kg bw by gavage in corn oil on 5 days per week for 103 weeks. Survival was significantly decreased in female mice at 750 mg/kg bw. In male mice, mean body weights were 6–14% lower in those at 750 mg/kg bw, and 4–8% lower in those at 375 mg/kg bw, compared with controls. In female mice, mean body weights in the group at 750 mg/kg bw were within 6% of the level in vehicle controls, while those of the group at 375 mg/kg bw were generally greater than the level in vehicle controls.

In female mice, treatment with 2-mercaptobenzothiazole resulted in an increase in the incidence of hepatocellular adenoma or carcinoma (combined) only at 375 mg/kg bw (4/50 [adjusted rate, 10.8%] controls; 12/49 [adjusted rate, 29.8%] at 375 mg/kg bw ($P = 0.035$ by the pairwise life-table test, $P = 0.028$ by pairwise incidental-tumour test) and 4/50 [adjusted rate, 18.2%] at 750 mg/kg bw). The historical incidence of

Table 3.1 Studies of carcinogenicity in experimental animals given 2-mercaptobenzothiazole by oral administration

| Species, strain (sex) Age at start Duration Reference | Purity Vehicle Dose regimen No. of animals at start No. of surviving animals | Incidence of tumours | Significance | Comments |
|---|---|---|---|---|
| Mouse, B6C3F ₁ (M+F, combined) 7 days 18 mo Innes et al. (1969)^a | Commercial product, "Captax" 0.5% gelatin (gavage) 0, 323 ppm Daily on days 7–35 (100 mg/kg bw), in the diet (0 or 323 ppm) for remainder 36/group 32, NR | Hepatomas, pulmonary tumours and lymphoma: NR | NS | Groups of 18 male and 18 female animals at start of study; the authors reported no significant increase in the incidence of hepatomas, pulmonary tumours, lymphoma or total tumours in treated mice |
| Mouse, C57BL/6 × AKR (M+F, combined) 7 days 18 mo Innes et al. (1969)^a | Commercial product, "Captax" 0.5% gelatin (gavage) 0, 323 ppm Daily gavage on days 7–35 (100 mg/kg bw), in the diet (0 or 323 ppm) for remainder 36/group 33, NR | Hepatomas, pulmonary tumours and lymphoma: NR | NS | Groups of 18 male and 18 female animals at start of study; the authors reported no significant increase in the incidence of hepatomas, pulmonary tumours, lymphoma or total tumours in treated mice |
| Mouse, B6C3F ₁ (M) 8 wks 103 wks NTP (1988)^b | Purity, 96.3% Corn oil 0, 375, 750 mg/kg bw by gavage 5 days/wk 50/group 38, 33, 30 | Any tumour type | NS | No evidence of carcinogenicity |
| Mouse, B6C3F ₁ (F) 8 wks 103 wks NTP (1988)^b | Purity, 96.3% Corn oil 0, 375, 750 mg/kg bw 5 days/wk 50/group 37, 39, 22 | <i>Liver</i> Hepatocellular adenoma: 3/50, 7/49, 4/50 Hepatocellular carcinoma: 1/50, 5/49, 0/50 Hepatocellular adenoma or carcinoma (combined): 4/50, 12/49, 4/50 | NS NS 375 mg/kg: pairwise $P = 0.035$ (life-table test), $P = 0.028$ (incidental-tumour test) | |

Table 3.1 (continued)

| Species, strain (sex) Age at start Duration Reference | Purity Vehicle Dose regimen No. of animals at start No. of surviving animals | Incidence of tumours | Significance | Comments |
|---|--|---|--|----------|
| Rat, F344 (M) 6–7 wks 103 wks NTP (1988)^b | Purity, 96.3% Corn oil 0, 375, 750 mg/kg bw by gavage 5 days/wk 50/group 42, 22, 20 | <i>Adrenal gland</i> Pheochromocytoma, benign or malignant: 18/50, 27/50, 24/49 Pheochromocytoma, benign: 18/50, 25/50, 22/49 Pheochromocytoma, malignant: 0/50, 2/50, 2/49 <i>Haematopoietic system</i> Mononuclear cell leukaemia: 7/50, 16/50, 3/50 <i>Pancreas</i> Acinar cell adenoma: 2/50, 13/50, 6/49 <i>Mesothelium</i> Mesothelioma (multiple organs): 0/50, 2/50, 3/50 <i>Preputial gland</i> Adenoma or carcinoma (combined): 1/50, 6/50, 5/50 | Trend, $P < 0.001$ (life-table test, $P = 0.038$ (incidental-tumour test); 375 mg/kg: pairwise $P < 0.001$ (life-table test), $P = 0.021$ (incidental-tumour test); 750 mg/kg: pairwise $P < 0.001$ (life-table test, $P = 0.034$ (incidental-tumour test). Trend, $P = 0.002$ (life-table test); 375 mg/kg: pairwise $P < 0.001$ (life-table test); 750 mg/kg: pairwise $P = 0.002$ (life-table test) NS 375 mg/kg: pairwise $P = 0.002$ (life-table test) Trend, $P = 0.017$ (life-table test); 375 mg/kg: pairwise $P < 0.001$ (life-table test), $P < 0.001$ (incidental-tumour test); 750 mg/kg: pairwise $P = 0.030$ (life-table test) Trend, $P = 0.039$ (life-table test), $P = 0.041$ (incidental-tumour test); historical corn oil vehicle controls NTP studies: 55/1450 (4% \pm 3%); range, 0–6/50 Trend, $P = 0.027$ (life-table test); 375 mg/kg: pairwise $P = 0.021$ (life-table test); 750 mg/kg: pairwise $P = 0.030$ (life-table test) | |

Table 3.1 (continued)

| Species, strain (sex) Age at start Duration Reference | Purity Vehicle Dose regimen No. of animals at start No. of surviving animals | Incidence of tumours | Significance | Comments |
|---|--|---|--|----------|
| Rat, F344 (M) 6–7 wks 103 wks NTP (1988) ^b (cont.) | | Adenoma: 0/50, 4/50, 4/50 Carcinoma: 1/50, 2/50, 1/50 <i>Pituitary gland</i> Adenoma: 14/50, 21/50, 12/48 <i>Skin, subcutaneous</i> Fibroma, neurofibroma, sarcoma, or fibrosarcoma (combined): 3/50, 6/50, 7/50 | Trend, $P = 0.016$ (life-table test), $P = 0.042$ (incidental-tumour test); 375 mg/kg: pairwise $P = 0.019$ (life-table test); 750 mg/kg: pairwise $P = 0.021$ (life-table test) NS 375 mg/kg: pairwise $P = 0.003$ (life-table test) Trend, $P = 0.031$ (life-table test); 750 mg/kg: pairwise $P = 0.037$ (life-table test); historical controls, corn oil vehicle, NTP studies: 126/1450 ($9\% \pm 4\%$) | |
| Rat, F344 (F) 6–7 wks 103 wks NTP (1988) ^b | Purity, 96.3% Corn oil 0, 188, 375 mg/kg bw by gavage 5 days/wk 50/group 28, 31, 25 | <i>Adrenal gland</i> Pheochromocytoma (benign): 1/50, 5/50, 6/50 <i>Pituitary gland</i> Adenoma: 15/49, 24/50, 25/50 Adenoma or adenocarcinoma (combined): 16/49, 24/50, 25/50 | Trend, $P = 0.030$ (life-table test), $P = 0.038$ (incidental-tumour test); 750 mg/kg: pairwise $P = 0.041$ (life-table test) Trend, $P = 0.014$ (life-table test), $P = 0.015$ (incidental-tumour test); 375 mg/kg: pairwise $P = 0.021$ (life-table test), $P = 0.027$ (incidental-tumour test) Trend, $P = 0.024$ (life-table test), $P = 0.028$ (incidental-tumour test); 375 mg/kg: pairwise $P = 0.036$ (life-table test); 1 (control) animal had a pituitary gland adenocarcinoma | |

^a Principal limitations of the study: inadequate reporting of results, limited macroscopic and microscopic evaluation, purity not reported and single dose tested

^b Principal strengths of the study: good laboratory practice, covers most of the lifespan, multiple doses tested and large number of animals per group
bw, body weight; F, female; M, male; mo, month; NR, not reported; NS, not significant; NTP, United States National Toxicology Program; wk, week

hepatocellular adenoma or carcinoma (combined) among female control mice in studies conducted by the National Toxicology Program (NTP) cited in the report was 116/1489 (8% ± 6%). The incidence of hepatocellular adenoma and hepatocellular carcinoma was 3/50 and 1/50 in the control group, 7/49 and 5/49 in the group at 375 mg/kg bw, and 4/50 and 0/50 at 750 mg/kg bw, respectively. In male mice, treatment with 2-mercaptobenzothiazole did not result in significant increases in tumour incidence, unusual tumours or early-onset tumours (NTP, 1988). [The strengths of this study included the large numbers of animals, compliance with good laboratory practice, the evaluation of multiple dose levels, and the duration of exposure that involved most of the lifespan.]

3.2 Rat

Oral administration

Groups of 50 male and 50 female Fischer 344/N rats (age, 6–7 weeks) were given 2-mercaptobenzothiazole (purity, 96.3%) at a dose of 0, 188 (females only), 375, or 750 (males only) mg/kg bw daily by gavage in corn oil on 5 days per week for 103 weeks. Survival was significantly decreased in male rats at 375 or 750 mg/kg bw. The mean body weights of treated males were similar to or greater than those of control males, and those of treated females were greater than those of control females.

In male rats, treatment with 2-mercaptobenzothiazole resulted in an increase in the incidence of pheochromocytoma of the adrenal gland (benign or malignant, combined) in the groups at 375 and 750 mg/kg bw: 18/50 controls, 27/50 at 375 mg/kg bw ($P < 0.001$ by the pairwise life-table test, $P = 0.021$ by the pairwise incidental-tumour test), and 24/49 at 750 mg/kg bw ($P < 0.001$ by the pairwise life-table test, $P = 0.034$ by the pairwise incidental-tumour test). Statistical analyses detected a positive dose-related trend

using the life-table ($P < 0.001$) and incidental-tumour ($P = 0.038$) tests. The reported historical incidence of benign or malignant pheochromocytoma (combined) in male control rats was 347/1442 (24% ± 9%). In addition, an increase in the incidence of benign pheochromocytoma was observed in treated males: 18/50 controls, 25/50 at 375 mg/kg bw ($P < 0.001$ by the pairwise life-table test), and 22/49 at 750 mg/kg bw ($P = 0.002$ by the pairwise life-table test). Statistical analyses detected a positive dose-related trend using the life-table test ($P = 0.002$). The incidence of malignant pheochromocytoma was 0/50 controls, 2/50 at 375 mg/kg bw, and 2/49 at 750 mg/kg bw. An increase in the incidence of mononuclear cell leukaemia of the haematopoietic system was also observed in the group at 375 mg/kg bw only (7/50 controls, 16/50 at 375 mg/kg bw ($P = 0.002$ by the pairwise life-table test) and 3/50 at 750 mg/kg bw). The reported historical incidence of mononuclear cell leukaemia in male control rats was 202/1450 (14% ± 8%). The incidence of pancreatic acinar cell adenoma was increased in treated males (2/50 controls, 13/50 at 375 mg/kg bw ($P < 0.001$ by the pairwise life-table test, $P < 0.001$ by the pairwise incidental-tumour test), and 6/49 at 750 mg/kg bw ($P = 0.030$ by the pairwise life-table test)). Statistical analyses detected a positive dose-related trend using the life-table test ($P = 0.017$), and the reported historical incidence of pancreatic acinar cell neoplasms in male control rats was 80/1381 (6% ± 8%). The incidence of preputial gland adenoma or carcinoma (combined) was also increased in treated males (1/50 controls, 6/50 at 375 mg/kg bw ($P = 0.021$ by the pairwise life-table test), and 5/50 at 750 mg/kg bw ($P = 0.030$ by the pairwise life-table test)). Statistical analyses detected a positive dose-related trend using the life-table test ($P = 0.027$), and the reported historical incidence of preputial gland adenoma or carcinoma (combined) in male control rats was 65/1450 (4% ± 4%). In addition, the treatment resulted in an increase in the incidence of preputial gland adenoma in males: 0/50

controls, 4/50 at 375 mg/kg bw ($P = 0.019$ by the pairwise life-table test), and 4/50 at 750 mg/kg bw ($P = 0.021$ by the pairwise life-table test). Statistical analyses detected a positive dose-related trend using the life-table ($P = 0.016$) and incidental tumour ($P = 0.042$) tests, but did not detect a positive dose-related trend or increases in the incidence of preputial gland carcinoma in individual treatment groups (1/50 controls, 2/50 at 375 mg/kg bw, and 1/50 at 750 mg/kg bw) using either the life-table or incidental-tumour tests. The reported historical incidence of carcinoma of the preputial gland in male control rats was 35/1450 ($2\% \pm 3\%$). A significant positive trend ($P = 0.041$ by the incidental-tumour test, $P = 0.039$ by the life-table test) in the incidence of mesothelioma (multiple organs) was observed (0/50 controls, 2/50 at 375 mg/kg bw, and 3/50 at 750 mg/kg bw). This increase was not statistically significant by pairwise comparison for either of the treated groups, and the incidence did not exceed that of historical corn-oil vehicle controls (55/1450, $4\% \pm 3\%$; reported range, 0–6/50). Also, an increase in the incidence of tumours of the skin (fibroma, neurofibroma, sarcoma, or fibrosarcoma combined) was observed in treated males (3/50 controls, 6/50 at 375 mg/kg bw, and 7/50 at 750 mg/kg bw ($P = 0.037$ by the pairwise life-table test)), and was associated with a significant positive trend ($P = 0.031$ by the life-table test). The incidence of adenoma of the pituitary gland was increased only at a dose of 375 mg/kg bw (14/50 controls, 21/50 at 375 mg/kg bw ($P = 0.003$ by the pairwise life-table test), and 12/48 at 750 mg/kg bw) with a reported historical incidence of 344/1411 ($24\% \pm 8\%$).

In female rats, treatment with 2-mercaptobenzothiazole resulted in an increase in the incidence of benign pheochromocytoma of the adrenal gland only at a dose of 375 mg/kg bw (1/50 controls, 5/50 at 188 mg/kg bw, and 6/50 at 375 mg/kg bw ($P = 0.041$ by the pairwise life-table test)). Statistical analyses detected a positive dose-related trend using the life-table

test ($P = 0.030$) and the incidental-tumour test ($P = 0.038$), and the reported historical incidence of benign pheochromocytoma in female controls was 82/1443 ($6\% \pm 4\%$). An increase in the incidence of adenoma of the pituitary gland was also observed in females at 375 mg/kg bw (15/49 controls, 24/50 at 188 mg/kg bw, and 25/50 at 375 mg/kg bw ($P = 0.021$ by the pairwise life-table test, $P = 0.027$ by the pairwise incidental-tumour test)). Statistical analyses detected a positive dose-related trend using the life-table ($P = 0.014$) and incidental-tumour ($P = 0.015$) tests. One rat in the control group had a pituitary adenocarcinoma. The reported historical incidence of adenoma, carcinoma, or adenocarcinoma (combined) of the pituitary gland in female control rats was 561/1407 ($40\% \pm 8\%$) ([NTP, 1988](#)). [The strengths of this study included the large numbers of animals, compliance with good laboratory practice, the evaluation of multiple dose levels, and the duration of exposure that involved most of the lifespan.]

4. Mechanistic and Other Relevant Data

4.1 Absorption, distribution, metabolism, excretion

4.1.1 Humans

2-Mercaptobenzothiazole has been detected in the urine samples of four workers employed at a plant producing 2-mercaptobenzothiazole, one worker from the administration department of the plant, and one out of forty persons not knowingly exposed to 2-mercaptobenzothiazole. Most 2-mercaptobenzothiazole in the urine was excreted in conjugated forms (e.g. 2-mercaptobenzothiazole glucuronide) rather than in its unchanged form ([Gries et al., 2015](#)).

4.1.2 Experimental systems

(a) Absorption, distribution, and excretion

An early study of pharmacokinetics after subcutaneous administration of radiolabelled 2-mercaptobenzothiazole to guinea-pigs demonstrated that the compound was well absorbed, with abrasion increasing the rate of absorption. Distribution occurred primarily in the kidney, liver, and thyroid gland. The thyroid gland contained the highest concentration of the compound 48 hours after injection. Ninety percent of the compound was conjugated with glucuronides and sulfates (cited in [NTP, 1988](#)).

When administered by gavage, the half-life of 2-mercaptobenzothiazole in Fischer 344 rats was less than 8 hours, possibly as short as 4–6 hours. Absorption was rapid and was not affected by doses up to 55 mg/kg bw. The major products of metabolism were polar metabolites, consistent with the findings of earlier studies in rats and guinea-pigs (cited in [NTP, 1988](#)).

After administration in Fischer 344 rats treated by gavage, 2-mercaptobenzothiazole-derived radioactivity in the blood decreased very little between 24 and 96 hours, suggesting that residual 2-mercaptobenzothiazole-derived material accumulated in the blood. After intravenous administration in Fischer 344 rats, whole blood, plasma, urine, and faeces were analysed for radioactivity at multiple time-points, from 5 minutes up to 72 hours. Most of the radiolabel (91–96%) was excreted in the urine and 4–15% in the faeces by 72 hours. A small amount (1.5–2%) remained in the erythrocytes. The metabolites found in the urine samples were the same as those found after gavage ([el Dareer et al., 1989](#)).

(b) Metabolism

In rats treated by intraperitoneal injection, the urinary metabolites of [³⁵S-mercapto]-2-mercaptobenzothiazole comprised glutathione and glucuronic acid conjugates, and inorganic sulfate ([Colucci & Buyske, 1965](#)).

4.2 Mechanisms of carcinogenesis

The evidence on the key characteristics of carcinogens ([Smith et al., 2016](#)), concerning whether 2-mercaptobenzothiazole modulates receptor-mediated effects and is genotoxic, is summarized below. Studies relevant to whether 2-mercaptobenzothiazole induces chronic inflammation are presented in Section 4.5.

4.2.1 Receptor-mediated effects

(a) Humans

No data were available to the Working Group.

(b) Experimental systems

The ability of leachates from rubber tyre materials to stimulate aryl hydrocarbon receptor (AhR)–DNA binding and AhR-dependent gene expression was recently demonstrated using recombinant mouse hepatoma (Hepa1c1c7)-based clonal cell lines containing a stably integrated AhR/dioxin-responsive element and a luciferase reporter gene with different intracellular locations and stabilities. Among the individual components of the leachates that might be involved in receptor-mediated effects, 2-mercaptobenzothiazole was identified as an AhR agonist ([He et al., 2011](#)).

2-Mercaptobenzothiazole has also been shown to inhibit rat and porcine thyroid peroxidase activity in vitro ([Paul et al., 2013](#)) and to interfere with the thyroid hormone pathway in a standard in-vivo protocol in larvae of the amphibian *Xenopus laevis* ([Tietge et al., 2013](#)). These findings were corroborated in a subsequent study that measured the inhibition of thyroid peroxidase derived from pig thyroid glands, and the inhibition of thyroxine release in a *X. laevis* thyroid gland explant culture assay and in a 7-day in-vivo assay in *X. laevis* ([Hornung et al., 2015](#)).

2-Mercaptobenzothiazole appears to accumulate in the rat thyroid after gavage ([el Dareer et al., 1989](#); see Section 4.1.2).

4.2.2 Genetic and related effects

See [Table 4.1](#) and [Table 4.2](#)

(a) Humans

No data in exposed humans were available to the Working Group.

In one study in vitro, 2-mercaptobenzothiazole did not induce micronucleus formation in human gastric and lung carcinoma cell lines (MGC-803 and A549, respectively) ([Ye et al., 2014](#)).

(b) Experimental systems

Zinc mercaptobenzothiazole, the zinc salt of 2-mercaptobenzothiazole, did not induce chromosomal aberrations in the bone marrow of Swiss albino mice 36 hours after administration of a single intraperitoneal dose of the compound. Groups of four mice received three different doses (480, 960, and 1920 µg/20 g) [24, 48 and 96 mg/kg bw] ([Mohanalan et al., 2000](#)).

In male and female Fischer 344 rats, 2-mercaptobenzothiazole (375 mg/kg bw by gavage) did not bind to DNA in any of the tissues examined (liver, adrenal glands, pituitary gland, pancreas, and bone marrow) ([Brewster et al., 1989](#)).

2-Mercaptobenzothiazole induced chromosomal aberrations and sister-chromatid exchange in Chinese hamster ovary (CHO) cells in the presence of a metabolic activation system, as well as mutations at the *Tk*^{+/-} locus in mouse L5178Y lymphoma cells ([NTP, 1988](#)). It also induced polyploidy in Chinese hamster lung (CHL) cells in the presence and absence of a metabolic activation system ([Matsuoka et al., 2005](#)). However, it gave negative results for the induction of 6-thioguanine-resistant mutants (*Hgprt* gene mutation) in Chinese hamster V79 cells ([Donner et al., 1983](#)).

2-Mercaptobenzothiazole was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, in the presence or absence

of metabolic activation ([NTP, 1988](#)). A previous study also reported negative results in *S. typhimurium*, although the purity of the compound and the dose were not specified ([Donner et al., 1983](#)). Similarly, 2-mercaptobenzothiazole was reported to give negative results in an early study in *Escherichia coli* SD-4-73, but the purity and doses tested were not indicated ([Szybalski, 1958](#)). More recently, 2-mercaptobenzothiazole also gave negative results when tested in *S. typhimurium* TA1535/psK1002 ([Ye et al., 2014](#)).

4.3 Data relevant to comparisons across agents and end-points

For all compounds evaluated in the present volume of the *IARC Monographs*, including 2-mercaptobenzothiazole, analyses of high-throughput screening data generated by the Tox21 and ToxCast™ research programmes of the government of the USA ([Kavlock et al., 2012](#); [Tice et al., 2013](#)) are presented in the *Monograph* on 1-bromopropane, in the present volume.

4.4 Susceptibility to cancer

No data were available to the Working Group.

4.5 Other adverse effects

4.5.1 Humans

The major effect of 2-mercaptobenzothiazole identified in humans is allergic contact dermatitis, which has been reported in numerous case studies after contact with synthetic rubber gloves ([Cao et al., 2010](#); [Tomc et al., 2012](#)), rubber ear plugs ([Deguchi & Tagami, 1996](#)), or condom catheters ([Harmon et al., 1995](#)), after working in the production of photographic films ([Rudzki et al., 1981](#)), or in a mining industry in which xanthate, carbamate and 2-mercaptobenzothiazole were used ([Sasseville et al., 2003](#)), after being issued

Table 4.1 Genetic and related effects of 2-mercaptobenzothiazole in human and other mammalian systems

| Species, strain, sex | Test system | End-point | Test | Results | | Dose (LED or HID) | Comments | Reference |
|-------------------------|--|--------------------|---------------------------|------------------------------|---------------------------|---|---|--|
| | | | | Without metabolic activation | With metabolic activation | | | |
| Human | Gastric MGC-803 and lung A549 cell lines | Chromosomal damage | Micronuclei | – | – | 100 µg/mL (not cytotoxic) | | Ye et al. (2014) |
| Mouse, Swiss albino, NR | Bone marrow | Chromosomal damage | Chromosomal aberrations | – | NA | 96 mg/kg bw i.p.; single dose (zinc salt of MBT) | | Mohanani et al. (2000) |
| Rat, Fischer 344, M/F | Liver, adrenal and pituitary glands, pancreas, bone marrow | DNA damage | DNA binding | – | NA | 375 mg/kg bw by gavage | | Brewster et al. (1989) |
| Mouse | L5178 lymphoma cells | Mutation | <i>Tk</i> ^{+/-} | – | + | 100 µg/mL without and 5 µg/mL with metabolic activation | | NTP (1988) |
| Chinese hamster | Lung (V79) | Mutation | <i>Hgp</i> <i>rt</i> | – | NT | 300 µg/mL | | Donner et al. (1983) |
| Chinese hamster | Lung (CHL) | Chromosomal damage | Chromosomal aberrations | + | + | 200 µg/mL without and 400 µg/mL with metabolic activation | Toxicity at 400 µg/mL without, and 600 µg/mL with, metabolic activation | Matsuoka et al. (2005) |
| Chinese hamster | Ovary (CHO) | Chromosomal damage | Chromosomal aberrations | – | + | 30 µg/mL without and 352 µg/mL with metabolic activation | | NTP (1988) |
| Chinese hamster | Ovary (CHO) | Chromosomal damage | Sister-chromatid exchange | – | + | 20 µg/mL without and 352 µg/mL with metabolic activation | | NTP (1988) |

+, positive; –, negative; bw, body weight; F, female; HID, highest ineffective dose; Hgp*rt*, hypoxanthine-guanine phosphoribosyltransferase; i.p., intraperitoneal; LED, lowest effective dose; M, male; MBT, 2-mercaptobenzothiazole; NA, not applicable; NR, not reported; NT, not tested; Tk, thymidine kinase locus

Table 4.2 Genetic and related effects of 2-mercaptobenzothiazole in non-mammalian systems

| Species, strain | End-point | Test | Results | | Concentration (LEC or HIC) | Comments | Reference |
|---|------------|----------------------|------------------------------|---------------------------|--|--|--------------------------------------|
| | | | Without metabolic activation | With metabolic activation | | | |
| <i>Salmonella typhimurium</i> , strain NR | Mutation | Reverse mutation | (-) | (-) | NR | Purity and dose NR; response stated to be statistically non-significant | Donner et al. (1983) |
| <i>Salmonella typhimurium</i> , TA100, TA1535, TA1537 | Mutation | Reverse mutation | - | - | 0–1000 µg/plate | | NTP (1988) |
| <i>Salmonella typhimurium</i> , TA98 | Mutation | Reverse mutation | - | ± | 0–1000 µg/plate | | NTP (1988) |
| <i>Salmonella typhimurium</i> , TA98, TA100, TA1535, TA1537 | Mutation | Reverse mutation | - | - | 0–10 000 µg/plate | | NTP (1988) |
| <i>Salmonella typhimurium</i> , TA1535/psK1002 | DNA damage | SOS/ <i>umu</i> test | - | - | 19 µg/mL without or 20 µg/mL with metabolic activation | 50% lethal concentration: 19 µg/mL without metabolic activation and 20 µg/ml with metabolic activation | Ye et al. (2014) |
| <i>Escherichia coli</i> , SD-4-73 | Mutation | Reverse mutation | (-) | NT | NR | Purity and dose NR | Szybalski (1958) |

+, positive; -, negative; (-), negative in a study of limited quality; ±, equivocal (variable response in several experiments within an adequate study); HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported; NT, not tested

with hand-based splints made of neoprene that is known to contain 2-mercaptobenzothiazole and its derivatives and formaldehyde (Stern et al., 1998), or after contact with an oil containing 2-mercaptobenzothiazole when making moulds (Wilkinson et al., 1990). The number of actual cases of allergic contact dermatitis attributed to mercapto mix and 2-mercaptobenzothiazole reported to EPIDERM in the United Kingdom from 1996 to 2012 was 177 (Warburton et al., 2015). An analysis of 803 female cleaners who were evaluated for contact dermatitis and 64 736 female controls without occupational dermatitis showed that the cleaners were significantly more frequently sensitized to 2-mercaptobenzothiazole (Liskowsky et al., 2011). In a positive patch-test analysis of 75 patients (38 men and 37 women) with contact allergic dermatitis, 6.66% (4 men and 1 woman) of the subjects tested showed reactivity to 2-mercaptobenzothiazole (Singhal & Reddy, 2000). Among 25 patients who showed a positive reaction to xanthates or other rubber additives, four patients showed reactivity to carbamate mix, thiuram mix, and 2-mercaptobenzothiazole, suggesting cross-reactivity of these chemicals (Sasseville et al., 2007). In 43 young people (31 men and 12 women) with eczematous skin lesions, two of the most frequent substances that showed a positive result in a patch test were thiurams (23.3%) and 2-mercaptobenazothiazole (20.9%) (Ventura et al., 2001).

In-vitro studies showed dose-dependent increases in cell-associated interleukin-18 in human skin cells (Corsini et al., 2009, 2013). In the human monocytic cell line THP-1, increased surface markers of CD54 and CD86 (An et al., 2009) and secretion of macrophage inflammatory protein-1 β was detected (Hirota & Moro, 2006).

4.5.2 Experimental systems

The major effects of 2-mercaptobenzothiazole other than carcinogenicity identified in a 2-year bioassay in rats were nephropathy characterized by tubular hyperplasia in exposed males, and ulcers and inflammation of the forestomach in exposed males and females (NTP, 1988). Cell proliferation in the draining lymph nodes was increased by exposure of mice to sensitizers, including 2-mercaptobenzothiazole (Ikarashi et al., 1993; Ahuja et al., 2009).

One study showed that haptentation occurs through the formation of mixed disulfides between the thiol group on 2-mercaptobenzothiazole and a protein sulfhydryl group (Chipinda et al., 2007). 2-Mercaptobenzothiazole can conjugate with lysine or cysteine (Wang & Tabor, 1988b). [The Working Group noted the possibility that the thiol group of 2-mercaptobenzothiazole may react either via oxidation and/or thioester formation with carboxylate groups of amino acids.]

5. Summary of Data Reported

5.1 Exposure data

2-Mercaptobenzothiazole is a chemical of high production volume that is mainly used as an accelerator in the manufacture of rubber products and as an inhibitor of corrosion. Workers are exposed during the production of 2-mercaptobenzothiazole, and can be exposed during the manufacture of tyres and rubber products and the production of pesticides. The general population is exposed to 2-mercaptobenzothiazole through dermal contact with consumer goods containing rubber. 2-Mercaptobenzothiazole has also been detected in samples of urban air, presumably originating from tyre abrasion, and in samples of effluent water from rubber manufacturers and tanneries.

5.2 Human carcinogenicity data

Studies on the carcinogenicity of 2-mercaptobenzothiazole were available for a plant that manufactured chemicals for the rubber industry in north Wales, United Kingdom, and for a general chemical manufacturing plant in West Virginia, USA.

The study on the plant in Wales was described in a series of reports. The Working Group considered that this study was the more informative of those available. Comparisons of exposed workers with the national population of England and Wales showed a significant excess of incident cases of cancer of the urinary bladder. Internal comparisons that controlled for other occupational exposures showed a non-significant trend in increasing incidence of cancer of the urinary bladder with increasing cumulative exposure to 2-mercaptobenzothiazole. A non-significant twofold excess risk was observed in the group with highest exposure.

The study in the plant in the USA reported a statistically significant fourfold excess of mortality from cancer of the urinary bladder based on a small number of deaths in a subgroup of workers exposed to 2-mercaptobenzothiazole, but with no documented exposure to 4-aminobiphenyl (classified in IARC Group 1 as a cause of cancer of the urinary bladder). A statistically significant trend in mortality from cancer of the urinary bladder with increasing cumulative exposure to 2-mercaptobenzothiazole was also observed.

The lack of available data on tobacco smoking was a limitation of both studies; however, confounding by smoking is unlikely to explain the exposure–response patterns observed in these studies.

5.3 Animal carcinogenicity data

2-Mercaptobenzothiazole was tested for carcinogenicity by oral administration in two studies in male and female mice (one of these studies was considered to be inadequate for an evaluation) and in one study in male and female rats.

In one study in male and female mice, oral administration (by gavage) of 2-mercaptobenzothiazole induced a significantly increased incidence of hepatocellular adenoma or carcinoma (combined) in female mice; in male mice, 2-mercaptobenzothiazole did not result in any significant increase in tumour incidence.

In the study in male and female rats, oral administration (by gavage) of 2-mercaptobenzothiazole to male rats induced a significantly increased incidence of benign pheochromocytoma and of pheochromocytoma (benign or malignant, combined) of the adrenal gland, with a significant positive trend, and was also associated with a significantly increased incidence of mononuclear cell leukaemia of the haematopoietic system, pancreatic acinar cell adenoma, preputial gland adenoma, preputial gland adenoma or carcinoma (combined), pituitary gland adenoma and tumours of the skin (fibroma, neurofibroma, sarcoma or fibrosarcoma, combined). A significant positive trend in the incidence of mesothelioma (multiple organs) was also observed. In female rats, oral administration (by gavage) of 2-mercaptobenzothiazole resulted in a significantly increased incidence of benign pheochromocytoma of the adrenal gland and of adenoma of the pituitary gland, with a significant positive trend.

5.4 Mechanistic and other relevant data

A study of workers reported urinary excretion of 2-mercaptobenzothiazole glucuronide. In rodents, the compound is well absorbed, and

distribution primarily to the kidney, liver, and thyroid gland occurs after subcutaneous administration. Urinary excretion accounts for > 90% after intravenous administration to rats. In rats, the major urinary metabolites are glutathione and glucuronic acid conjugates.

With respect to the key characteristics of human carcinogens, there is *moderate* evidence that 2-mercaptobenzothiazole modulates receptor-mediated effects. 2-Mercaptobenzothiazole acted as an agonist of the aryl hydrocarbon receptor in an assay in mouse hepatoma cells. 2-Mercaptobenzothiazole also inhibited rat and pig thyroid peroxidase in vitro, and inhibited thyroxine release from *Xenopus laevis* thyroid gland ex vivo and in vivo. ToxCast data supported activation of the aryl hydrocarbon receptor pathway by 2-mercaptobenzothiazole in human cells and in assays for development in zebrafish.

There is *weak* evidence that 2-mercaptobenzothiazole is genotoxic. 2-Mercaptobenzothiazole induced chromosomal aberrations and sister-chromatid exchange in Chinese hamster ovary cells in the presence of a metabolic activation system, and caused mutations at the *Tk* locus in mouse L5178Y lymphoma cells. However, it was not mutagenic in test systems in bacteria or in human gastric and lung carcinoma cell lines, and did not bind to rat DNA in vivo.

The evidence that 2-mercaptobenzothiazole induces chronic inflammation is *weak*. 2-Mercaptobenzothiazole is a contact allergen in humans. It increased the levels of interleukin-18 in human skin cells, and caused inflammation of the forestomach in male and female rats in a 2-year bioassay.

There were few data on the other key characteristics of human carcinogens (is electrophilic or can be metabolically activated, alters DNA repair or causes genomic instability, induces epigenetic alterations, induces oxidative stress, is immunosuppressive, causes immortalization, or alters cell proliferation, cell death, or nutrient supply).

6. Evaluation

6.1 Cancer in humans

There is *limited evidence* in humans for the carcinogenicity of 2-mercaptobenzothiazole. A positive association has been observed between exposure to 2-mercaptobenzothiazole and cancer of the urinary bladder.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 2-mercaptobenzothiazole.

6.3 Overall evaluation

2-Mercaptobenzothiazole is *probably carcinogenic to humans* (Group 2A).

References

- Ahuja V, Wanner R, Platzek T, Stahlmann R (2009). Appraisal of the sensitizing potential of orally and dermally administered mercaptobenzothiazole by a biphasic protocol of the local lymph node assay. *Arch Toxicol*, 83(10):933–9. doi:[10.1007/s00204-009-0426-y](https://doi.org/10.1007/s00204-009-0426-y) PMID:[19381614](https://pubmed.ncbi.nlm.nih.gov/19381614/)
- Airaudo CB, Gayte-Sorbier A, Momburg R, Laurent P (1990). Leaching of antioxidants and vulcanization accelerators from rubber closures into drug preparations. *J Biomater Sci Polym Ed*, 1(4):231–41. doi:[10.1163/156856289X00127](https://doi.org/10.1163/156856289X00127) PMID:[2279005](https://pubmed.ncbi.nlm.nih.gov/2279005/)
- An S, Kim S, Huh Y, Lee TR, Kim HK, Park KL et al. (2009). Expression of surface markers on the human monocytic leukaemia cell line, THP-1, as indicators for the sensitizing potential of chemicals. *Contact Dermat*, 60(4):185–92. doi:[10.1111/j.1600-0536.2009.01528.x](https://doi.org/10.1111/j.1600-0536.2009.01528.x) PMID:[19338585](https://pubmed.ncbi.nlm.nih.gov/19338585/)
- Ancona A, Suárez de la Torre R, Evia JR (1985). Dermatitis from mercaptobenzothiazole in a Foley catheter. *Contact Dermat*, 13(5):339–40. doi:[10.1111/j.1600-0536.1985.tb02596.x](https://doi.org/10.1111/j.1600-0536.1985.tb02596.x) PMID:[4092457](https://pubmed.ncbi.nlm.nih.gov/4092457/)
- Avagyan R, Sadiktsis I, Bergvall C, Westerholm R (2014). Tire tread wear particles in ambient air—a previously unknown source of human exposure to the biocide

- 2-mercaptobenzothiazole. *Environ Sci Pollut Res Int*, 21(19):11580–6. doi:[10.1007/s11356-014-3131-1](https://doi.org/10.1007/s11356-014-3131-1) PMID:[25028318](https://pubmed.ncbi.nlm.nih.gov/25028318/)
- Azam MA, Suresh B (2012). Biological activities of 2-mercaptobenzothiazole derivatives: a review. *Sci Pharm*, 80(4):789–823. doi:[10.3797/scipharm.1204-27](https://doi.org/10.3797/scipharm.1204-27) PMID:[23264933](https://pubmed.ncbi.nlm.nih.gov/23264933/)
- Barnes KA, Castle L, Damant AP, Read WA, Speck DR (2003). Development and application of an LC-MS method to determine possible migration of mercaptobenzothiazole, benzothiazole and related vulcanization residues from rubber used in contact with food and drink. *Food Addit Contam*, 20(2):196–205. doi:[10.1080/0265203021000044876](https://doi.org/10.1080/0265203021000044876) PMID:[12623669](https://pubmed.ncbi.nlm.nih.gov/12623669/)
- Bauer A, Geier J, Mahler V, Uter W (2015). [Contact allergies in the German workforce : Data of the IVDK network from 2003-2013.] *Hautarzt*, 66(9):652–64. [German] doi:[10.1007/s00105-015-3660-7](https://doi.org/10.1007/s00105-015-3660-7) PMID:[26228172](https://pubmed.ncbi.nlm.nih.gov/26228172/)
- Bergendorff O, Persson C, Hansson C (2006). High-performance liquid chromatography analysis of rubber allergens in protective gloves used in health care. *Contact Dermat*, 55(4):210–5. doi:[10.1111/j.1600-0536.2006.00912.x](https://doi.org/10.1111/j.1600-0536.2006.00912.x) PMID:[16958918](https://pubmed.ncbi.nlm.nih.gov/16958918/)
- Bouma K, Nab FM, Schothorst RC (2003). Migration of N-nitrosamines, N-nitrosatable substances and 2-mercaptobenzothiazole from baby bottle teats and soothers: a Dutch retail survey. *Food Addit Contam*, 20(9):853–8. doi:[10.1080/0265203031000156105](https://doi.org/10.1080/0265203031000156105) PMID:[13129781](https://pubmed.ncbi.nlm.nih.gov/13129781/)
- Breuer D, Fischer P, Hansen K (2002). Benzotriazoles (1,2,3-benzotriazole, 5-methyl-1H-benzotriazole, 5,6-dimethylbenzotriazole). In: The MAK collection for occupational health and safety, air monitoring methods, vol. 8, p. 61–80. Available from: <http://onlinelibrary.wiley.com/book/10.1002/3527600418/topics>.
- Brewster DW, Mirly KJ, Wilson AG, Barnett JW Jr (1989). Lack of in vivo DNA binding of mercaptobenzothiazole to selected tissues of the rat. *Biochem Biophys Res Commun*, 165(1):342–8. doi:[10.1016/0006-291X\(89\)91075-9](https://doi.org/10.1016/0006-291X(89)91075-9) PMID:[2590232](https://pubmed.ncbi.nlm.nih.gov/2590232/)
- Cao LY, Taylor JS, Sood A, Murray D, Siegel PD (2010). Allergic contact dermatitis to synthetic rubber gloves: changing trends in patch test reactions to accelerators. *Arch Dermatol*, 146(9):1001–7. doi:[10.1001/archdermatol.2010.219](https://doi.org/10.1001/archdermatol.2010.219) PMID:[20855699](https://pubmed.ncbi.nlm.nih.gov/20855699/)
- Carreón T, Hein MJ, Hanley KW, Viet SM, Ruder AM (2014). Bladder cancer incidence among workers exposed to o-toluidine, aniline and nitrobenzene at a rubber chemical manufacturing plant. *Occup Environ Med*, 71(3):175–82. doi:[10.1136/oemed-2013-101873](https://doi.org/10.1136/oemed-2013-101873) PMID:[24368697](https://pubmed.ncbi.nlm.nih.gov/24368697/)
- Chang JY, Xiao NJ, Zhu M, Zhang J, Hoff E, Russell SJ et al. (2010). Leachables from saline-containing IV bags can alter therapeutic protein properties. *Pharm Res*, 27(11):2402–13. doi:[10.1007/s11095-010-0193-8](https://doi.org/10.1007/s11095-010-0193-8) PMID:[20585844](https://pubmed.ncbi.nlm.nih.gov/20585844/)
- Chipinda I, Hettick JM, Simoyi RH, Siegel PD (2007). Oxidation of 2-mercaptobenzothiazole in latex gloves and its possible haptentation pathway. *Chem Res Toxicol*, 20(8):1084–92. doi:[10.1021/tx700139g](https://doi.org/10.1021/tx700139g) PMID:[17630704](https://pubmed.ncbi.nlm.nih.gov/17630704/)
- Chowdhuri S, Ghosh S (2007). Epidemio-allergological study in 155 cases of footwear dermatitis. *Indian J Dermatol Venereol Leprol*, 73(5):319–22. doi:[10.4103/0378-6323.34011](https://doi.org/10.4103/0378-6323.34011) PMID:[17921611](https://pubmed.ncbi.nlm.nih.gov/17921611/)
- Collins JJ, Strauss ME, Riordan SG (1999). Mortalities of workers at the Nitro plant with exposure to 2-mercaptobenzothiazole. *Occup Environ Med*, 56(10):667–71. doi:[10.1136/oem.56.10.667](https://doi.org/10.1136/oem.56.10.667) PMID:[10658544](https://pubmed.ncbi.nlm.nih.gov/10658544/)
- Colucci DF, Buyske DA (1965). The biotransformation of a sulfonamide to a mercaptan and to mercapturic acid and glucuronide conjugates. *Biochem Pharmacol*, 14(4):457–66. doi:[10.1016/0006-2952\(65\)90218-2](https://doi.org/10.1016/0006-2952(65)90218-2) PMID:[14322970](https://pubmed.ncbi.nlm.nih.gov/14322970/)
- Corsini E, Galbiati V, Mitjans M, Galli CL, Marinovich M (2013). NCTC 2544 and IL-18 production: a tool for the identification of contact allergens. *Toxicol In Vitro*, 27(3):1127–34. doi:[10.1016/j.tiv.2012.05.018](https://doi.org/10.1016/j.tiv.2012.05.018) PMID:[23063874](https://pubmed.ncbi.nlm.nih.gov/23063874/)
- Corsini E, Mitjans M, Galbiati V, Lucchi L, Galli CL, Marinovich M (2009). Use of IL-18 production in a human keratinocyte cell line to discriminate contact sensitizers from irritants and low molecular weight respiratory allergens. *Toxicol In Vitro*, 23(5):789–96. doi:[10.1016/j.tiv.2009.04.005](https://doi.org/10.1016/j.tiv.2009.04.005) PMID:[19397996](https://pubmed.ncbi.nlm.nih.gov/19397996/)
- Cox GB (1976). Determination of 2-mercaptobenzothiazole in waste dump effluent by high-pressure liquid chromatography. *J Chromatogr A*, 116(1):244–7. doi:[10.1016/S0021-9673\(00\)83731-0](https://doi.org/10.1016/S0021-9673(00)83731-0)
- Deguchi M, Tagami H (1996). Contact dermatitis of the ear due to a rubber earplug. *Dermatology*, 193(3):251–2. doi:[10.1159/000246257](https://doi.org/10.1159/000246257) PMID:[8944351](https://pubmed.ncbi.nlm.nih.gov/8944351/)
- Dickel H, Kuss O, Schmidt A, Diepgen TL (2002). Occupational relevance of positive standard patch-test results in employed persons with an initial report of an occupational skin disease. *Int Arch Occup Environ Health*, 75(6):423–34. doi:[10.1007/s00420-002-0328-2](https://doi.org/10.1007/s00420-002-0328-2) PMID:[12070639](https://pubmed.ncbi.nlm.nih.gov/12070639/)
- Donner M, Husgafvel-Pursiainen K, Jenssen D, Rannug A (1983). Mutagenicity of rubber additives and curing fumes. Results from five short-term bioassays. *Scand J Work Environ Health*, 9:Suppl 2: 27–37. PMID:[6415811](https://pubmed.ncbi.nlm.nih.gov/6415811/)
- ECHA (2012). 2-Mercaptobenzothiazole. CAS No. 149-30-4. Registered substances [online database]. Helsinki, Finland: European Chemicals Agency. Available from: <https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/13432>.
- ECHA (2015). Registered substance benzothiazole-2-thiol (2-MBT), Information on chemicals. Helsinki, Finland: European Chemicals Agency. Available from: <http://echa.europa.eu/information-on-chemicals>.

- el Dareer SM, Kalin JR, Tillery KF, Hill DL, Barnett JW Jr (1989). Disposition of 2-mercaptobenzothiazole and 2-mercaptobenzothiazole disulfide in rats dosed intravenously, orally, and topically and in guinea pigs dosed topically. *J Toxicol Environ Health*, 27(1):65–84. doi:[10.1080/15287398909531279](https://doi.org/10.1080/15287398909531279) PMID:2724369
- EPA (1993). Method 640. The determination of mercaptobenzothiazole in municipal and industrial wastewaters. In: Methods for the determination of nonconventional pesticides in municipal and industrial wastewater, Vol. 1, EPA Publication 821R93010A. United States Environmental Protection Agency.
- EPA (1994). R.E.D. facts. Sodium and zinc salts of 2-mercaptobenzothiazole. Report No. EPA-738-F-94-024. United States Environmental Protection Agency. Available from: <http://archive.epa.gov/pesticides/reregistration/web/pdf/2380fact.pdf>.
- EPA (2012). Chemical data reporting under the Toxic Substances Control Act. Non-confidential 2012 chemical data reporting information on chemical production and use in the United States. United States Environmental Protection Agency. Available from: <http://www2.epa.gov/chemical-data-reporting>.
- Federal Register (2000). Federal Register, 65(248) (December 26, 2000) (65FR81686). Available from: <http://www.gpo.gov/fdsys/granule/FR-2000-12-26/00-32498>
- Foussereau J, Muslmani M, Cavelier C, Herve-Bazin B (1986). Contact allergy to safety shoes. *Contact Dermat*, 14(4):233–6. doi:[10.1111/j.1600-0536.1986.tb01231.x](https://doi.org/10.1111/j.1600-0536.1986.tb01231.x) PMID:2941221
- Geier J, Lessmann H, Mahler V, Pohrt U, Uter W, Schnuch A (2012). Occupational contact allergy caused by rubber gloves—nothing has changed. *Contact Dermat*, 67(3):149–56. doi:[10.1111/j.1600-0536.2012.02139.x](https://doi.org/10.1111/j.1600-0536.2012.02139.x) PMID:22762249
- GESTIS (2015). GESTIS DNEL Database [online database]. GESTIS international limit values. Available from: [http://dnel-en.itrust.de/nxt/gateway.dll/dnel_en/000000.xml?f=templates\\$fn=default.htm\\$vid=dneleng:ddebeng\\$3.0/](http://dnel-en.itrust.de/nxt/gateway.dll/dnel_en/000000.xml?f=templates$fn=default.htm$vid=dneleng:ddebeng$3.0/), accessed March 2016.
- Gries W, Küpper K, Leng G (2015). Rapid and sensitive LC-MS-MS determination of 2-mercaptobenzothiazole, a rubber additive, in human urine. *Anal Bioanal Chem*, 407(12):3417–23. doi:[10.1007/s00216-015-8533-5](https://doi.org/10.1007/s00216-015-8533-5) PMID:25701422
- GuideChem (2015). CAS No. 149-30-4 (2-mercaptobenzothiazole (MBT)). GuideChem. Chemical trading guide. Available from: <http://www.guidechem.com/cas-149/149-30-4.html>, accessed 19 January 2016.
- Hamilton G (1987). Contamination of contrast agent by MBT in rubber seals. *CMAJ*, 136(10):1020–1. PMID:3567758
- Harmon CB, Connolly SM, Larson TR (1995). Condom-related allergic contact dermatitis. *J Urol*, 153(4):1227–8. doi:[10.1016/S0022-5347\(01\)67561-X](https://doi.org/10.1016/S0022-5347(01)67561-X) PMID:7869508
- He G, Zhao B, Denison MS (2011). Identification of benzothiazole derivatives and polycyclic aromatic hydrocarbons as aryl hydrocarbon receptor agonists present in tire extracts. *Environ Toxicol Chem*, 30(8):1915–25. doi:[10.1002/etc.581](https://doi.org/10.1002/etc.581) PMID:21590714
- Hirota M, Moro O (2006). MIP-1beta, a novel biomarker for in vitro sensitization test using human monocytic cell line. *Toxicol In Vitro*, 20(5):736–42. doi:[10.1016/j.tiv.2005.10.013](https://doi.org/10.1016/j.tiv.2005.10.013) PMID:16314067
- Hornung MW, Kosian PA, Haselman JT, Korte JJ, Challis K, Macherla C et al. (2015). In vitro, ex vivo, and in vivo determination of thyroid hormone modulating activity of benzothiazole s. *Toxicol Sci*, 146(2):254–64. doi:[10.1093/toxsci/kfv090](https://doi.org/10.1093/toxsci/kfv090) PMID:25953703
- HSDB (2015). Dimethyl-p-toluidine. CASRN: 99-97-8. Hazardous Substances Data Bank. United States National Library of Medicine. Available from: <http://toxnet.nlm.nih.gov/>, accessed February 2016.
- IFA (2015). GESTIS substance database. Information system on hazardous substances of the German Social Accident Insurance. Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA). Available from: www.dguv.de/ifa/GESTIS/GESTIS-Stoffdatenbank/.
- Ikarashi Y, Tsuchiya T, Nakamura A (1993). Evaluation of contact sensitivity of rubber chemicals using the murine local lymph node assay. *Contact Dermat*, 28(2):77–80. doi:[10.1111/j.1600-0536.1993.tb03345.x](https://doi.org/10.1111/j.1600-0536.1993.tb03345.x) PMID:8384542
- Innes JR, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER et al. (1969). Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note. *J Natl Cancer Inst*, 42(6):1101–14. PMID:5793189
- Jung P, Sesztak-Greinecker G, Wantke F, Götz M, Jarisch R, Hemmer W (2006). Bikini dermatitis due to mercaptobenzothiazole. *Contact Dermat*, 54(6):345–6. doi:[10.1111/j.0105-1873.2006.0645c.x](https://doi.org/10.1111/j.0105-1873.2006.0645c.x) PMID:16787458
- Jungclaus GA, Games LM, Hites RA (1976). Identification of trace organic compounds in tire manufacturing plant wastewaters. *Anal Chem*, 48(13):1894–6. doi:[10.1021/ac50007a021](https://doi.org/10.1021/ac50007a021) PMID:970644
- Kavlock R, Chandler K, Houck K, Hunter S, Judson R, Kleinstreuer N et al. (2012). Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol*, 25(7):1287–302. doi:[10.1021/tx3000939](https://doi.org/10.1021/tx3000939) PMID:22519603
- Keith LH (1976). Identification of organic compounds in unbleached treated kraft paper mill waste waters. *Environ Sci Technol*, 10(6):555–64. doi:[10.1021/es60117a009](https://doi.org/10.1021/es60117a009)
- Khoroshko LO, Petrova VN, Viktorovskii IV, Lahtiperä M, Sinkkonen S, Paasivirta J (2005). A wood preservative metabolite in river water. *Environ Sci Pollut Res Int*, 12(1):8–9. doi:[10.1065/espr2004.11.224](https://doi.org/10.1065/espr2004.11.224) PMID:15768735

- Howe-Grant M, editor (1982). Kirk-Othmer. Encyclopedia of chemical technology. 3rd ed. John Wiley and Sons.
- Kloepfer A, Gnirss R, Jekel M, Reemtsma T (2004b). Occurrence of benzothiazoles in municipal wastewater and their fate in biological treatment. *Water Sci Technol*, 50(5):203–8. Available from: https://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15497849&dopt=Abstract. PMID:15497849
- Kloepfer A, Jekel M, Reemtsma T (2004a). Determination of benzothiazoles from complex aqueous samples by liquid chromatography-mass spectrometry following solid-phase extraction. *J Chromatogr A*, 1058(1-2):81–8. doi:10.1016/S0021-9673(04)01437-2 PMID:15595654
- Liskowsky J, Geier J, Bauer A (2011). Contact allergy in the cleaning industry: analysis of contact allergy surveillance data of the Information Network of Departments of Dermatology. *Contact Dermat*, 65(3):159–66. doi:10.1111/j.1600-0536.2011.01937.x PMID:21679195
- Llompert M, Sanchez-Prado L, Pablo Lamas J, Garcia-Jares C, Roca E, Dagnac T (2013). Hazardous organic chemicals in rubber recycled tire playgrounds and pavers. *Chemosphere*, 90(2):423–31. doi:10.1016/j.chemosphere.2012.07.053 PMID:22921644
- Manninen A, Auriola S, Vartiainen M, Liesivuori J, Turunen T, Pasanen M (1996). Determination of urinary 2-mercaptobenzothiazole (2-MBT), the main metabolite of 2-(thiocyanomethylthio)benzothiazole (TCMTB) in humans and rats. *Arch Toxicol*, 70(9):579–84. doi:10.1007/s002040050315 PMID:8831908
- Matsuoka A, Isama K, Tsuchiya T (2005). In vitro induction of polyploidy and chromatid exchanges by culture medium extracts of natural rubbers compounded with 2-mercaptobenzothiazole as a positive control candidate for genotoxicity tests. *J Biomed Mater Res A*, 75(2):439–44. doi:10.1002/jbm.a.30442 PMID:16088893
- Mohan PV, Joseph R, Ramesh P, Rathinam K (2000). Assessment of in vivo chromosomal aberrations–potency of zinc mercapto benzo thiazole. *J Biomater Appl*, 14(3):224–8. doi:10.1177/088532820001400302 PMID:10656541
- National Toxicology Program (1988). NTP toxicology and carcinogenesis studies of 2-mercaptobenzothiazole (CAS No. 149-30-4) in F344/N rats and B6C3F1 mice (gavage studies). *Natl Toxicol Program Tech Rep Ser*, 332:1–172. Available from: http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr332.pdf. PMID:12732904
- NIOSH (1989). Goodyear Tire and Rubber Company, Niagara Falls, NY. Interim report No. 1. NIOSH Report HETA 88-159. Cincinnati (OH), USA: United States Department of Health and Human Services, Public Health Service, Centers for Disease Control, Public Health Service, National Institute for Occupational Safety and Health; pp. 1–31.
- NIOSH (1992). Goodyear Tire and Rubber Company, Niagara Falls, NY. Interim report No. 2. NIOSH Report HETA 88-159. Cincinnati (OH), USA: United States Department of Health and Human Services, Public Health Service, Centers for Disease Control, Public Health Service, National Institute for Occupational Safety and Health; pp. 1–113.
- OECD (2004). The 2004 OECD list of high production volume chemicals. Paris, France: Organisation for Economic Co-operation and Development. Available from: <http://www.oecd.org/chemicalsafety/risk-assessment/33883530.pdf>.
- Parham H, Aibaghi B, Ghasemi J (2008). Simultaneous square wave voltammetric determination of 2-mercaptobenzothiazole and 2-mercaptobenzoxazole by partial least squares method in water samples. *J Hazard Mater*, 151(2-3):636–41. doi:10.1016/j.jhazmat.2007.06.036 PMID:17651895
- Parham H, Khoshnam F (2013). Solid phase extraction-preconcentration and high performance liquid chromatographic determination of 2-mercapto-(benzothiazole, benzoxazole and benzimidazole) using copper oxide nanoparticles. *Talanta*, 114:90–4. doi:10.1016/j.talanta.2013.04.014 PMID:23953446
- Parham H, Pourreza N, Marahel F (2015). Resonance Rayleigh scattering method for determination of 2-mercaptobenzothiazole using gold nanoparticles probe. *Spectrochim Acta A Mol Biomol Spectrosc*, 151:308–14. doi:10.1016/j.saa.2015.06.108 PMID:26143323
- Paul KB, Hedge JM, Macherla C, Filer DL, Burgess E, Simmons SO et al. (2013). Cross-species analysis of thyroperoxidase inhibition by xenobiotics demonstrates conservation of response between pig and rat. *Toxicology*, 312:97–107. doi:10.1016/j.tox.2013.08.006 PMID:23959146
- Reemtsma T (2000). Determination of 2-substituted benzothiazoles of industrial use from water by liquid chromatography/electrospray ionization tandem mass spectrometry. *Rapid Commun Mass Spectrom*, 14(17):1612–8. doi:10.1002/1097-0231(20000915)14:17<1612::AID-RCM70>3.0.CO;2-C PMID:10960915
- Reepmeyer JC, Juhl YH (1983). Contamination of injectable solutions with 2-mercaptobenzothiazole leached from rubber closures. *J Pharm Sci*, 72(11):1302–5. doi:10.1002/jps.2600721117 PMID:6644593
- Rodríguez DM, Wrobel K, Jiménez MG, Wrobel K (2004). Determination of 2-mercaptobenzothiazole (MBT) in tannery wastewater by high performance liquid chromatography with amperometric detection. *Bull Environ Contam Toxicol*, 73(5):818–24. doi:10.1007/s00128-004-0500-3 PMID:15669724
- Rudzki E, Napiórkowska T, Czerwińska-Dihm I (1981). Dermatitis from 2-mercaptobenzothiazole in photographic films. *Contact Dermat*, 7(1):43. doi:10.1111/j.1600-0536.1981.tb03958.x PMID:6454535

- Sasseville D, Al-Sowaidi M, Moreau L (2007). Cross-reactions between xanthates and rubber additives. *Dermatitis*, 18(3):150–4. doi:[10.2310/6620.2007.06020](https://doi.org/10.2310/6620.2007.06020) PMID:[17725922](https://pubmed.ncbi.nlm.nih.gov/17725922/)
- Sasseville D, Muhn CY, Al-Sowaidi M (2003). Occupational allergic contact dermatitis from xanthates and carbamates in mining processes. *Am J Contact Dermat*, 14(3):166–8. PMID:[14744410](https://pubmed.ncbi.nlm.nih.gov/14744410/)
- Schmitt TM, Muzher ES (1981). Determination of 2-mercaptobenzothiazole, tolyltriazole and benzotriazole in coolant formulations by liquid chromatography. *Talanta*, 28(10):777–9. doi:[10.1016/0039-9140\(81\)80123-3](https://doi.org/10.1016/0039-9140(81)80123-3) PMID:[18963003](https://pubmed.ncbi.nlm.nih.gov/18963003/)
- Shackelford WM, Cline DM, Faas L, Kurth G (1983). An evaluation of automated spectrum matching for survey identification of wastewater components by gas chromatography—mass spectrometry *Anal Chim Acta*, 146:15–27. [Supplementary data] doi:[10.1016/S0003-2670\(00\)80588-7](https://doi.org/10.1016/S0003-2670(00)80588-7)
- Singhal V, Reddy BS (2000). Common contact sensitizers in Delhi. *J Dermatol*, 27(7):440–5. doi:[10.1111/j.1346-8138.2000.tb02202.x](https://doi.org/10.1111/j.1346-8138.2000.tb02202.x) PMID:[10935340](https://pubmed.ncbi.nlm.nih.gov/10935340/)
- Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I et al. (2016). Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect*, 124(6):713–21. PMID:[26600562](https://pubmed.ncbi.nlm.nih.gov/26600562/)
- Sorahan T (2008). Bladder cancer risks in workers manufacturing chemicals for the rubber industry. *Occup Med (Lond)*, 58(7):496–501. doi:[10.1093/occmed/kqn104](https://doi.org/10.1093/occmed/kqn104) PMID:[18725381](https://pubmed.ncbi.nlm.nih.gov/18725381/)
- Sorahan T (2009). Cancer risks in chemical production workers exposed to 2-mercaptobenzothiazole. *Occup Environ Med*, 66(4):269–73. doi:[10.1136/oem.2008.041400](https://doi.org/10.1136/oem.2008.041400) PMID:[19158128](https://pubmed.ncbi.nlm.nih.gov/19158128/)
- Sorahan T, Hamilton L, Jackson JR (2000). A further cohort study of workers employed at a factory manufacturing chemicals for the rubber industry, with special reference to the chemicals 2-mercaptobenzothiazole (MBT), aniline, phenyl-beta-naphthylamine and o-toluidine. *Occup Environ Med*, 57(2):106–15. doi:[10.1136/oem.57.2.106](https://doi.org/10.1136/oem.57.2.106) PMID:[10711278](https://pubmed.ncbi.nlm.nih.gov/10711278/)
- Sorahan T, Pope D (1993). Mortality study of workers employed at a plant manufacturing chemicals for the rubber industry: 1955–86. *Br J Ind Med*, 50(11):998–1002. PMID:[8280636](https://pubmed.ncbi.nlm.nih.gov/8280636/)
- Stern EB, Callinan N, Hank M, Lewis EJ, Schousboe JT, Ytterberg SR (1998). Neoprene splinting: dermatological issues. *Am J Occup Ther*, 52(7):573–8. doi:[10.5014/ajot.52.7.573](https://doi.org/10.5014/ajot.52.7.573) PMID:[9693703](https://pubmed.ncbi.nlm.nih.gov/9693703/)
- Strauss ME, Barrick ED, Bannister RM (1993). Mortality experience of employees exposed to 2-mercaptobenzothiazole at a chemical plant in Nitro, West Virginia. *Br J Ind Med*, 50(10):888–93. PMID:[8217846](https://pubmed.ncbi.nlm.nih.gov/8217846/)
- Szybalski W (1958). Special microbiological systems. II. Observations on chemical mutagenesis in microorganisms. *Ann N Y Acad Sci*, 76(3):475–89. doi:[10.1111/j.1749-6632.1958.tb57106.x](https://doi.org/10.1111/j.1749-6632.1958.tb57106.x) PMID:[13627873](https://pubmed.ncbi.nlm.nih.gov/13627873/)
- Tice RR, Austin CP, Kavlock RJ, Bucher JR (2013). Improving the human hazard characterization of chemicals: a Tox21 update. *Environ Health Perspect*, 121(7):756–65. doi:[10.1289/ehp.1205784](https://doi.org/10.1289/ehp.1205784) PMID:[23603828](https://pubmed.ncbi.nlm.nih.gov/23603828/)
- Tietge JE, Degitz SJ, Haselman JT, Butterworth BC, Korte JJ, Kosian PA et al. (2013). Inhibition of the thyroid hormone pathway in *Xenopus laevis* by 2-mercaptobenzothiazole. *Aquat Toxicol*, 126:128–36. doi:[10.1016/j.aquatox.2012.10.013](https://doi.org/10.1016/j.aquatox.2012.10.013) PMID:[23178179](https://pubmed.ncbi.nlm.nih.gov/23178179/)
- Tomc C, Kwasniak L, Shoureshi P, Nedorost S (2012). Allergic contact dermatitis probably caused by mercaptobenzothiazole in thermal undergarments. *Contact Dermat*, 66(5):294–5. doi:[10.1111/j.1600-0536.2012.02009.x](https://doi.org/10.1111/j.1600-0536.2012.02009.x) PMID:[22486572](https://pubmed.ncbi.nlm.nih.gov/22486572/)
- Ventura MT, Dagnello M, Martino MG, Di Corato R, Giuliano G, Tursi A (2001). Contact dermatitis in students practicing sports: incidence of rubber sensitisation. *Br J Sports Med*, 35(2):100–2. doi:[10.1136/bjbm.35.2.100](https://doi.org/10.1136/bjbm.35.2.100) PMID:[11273970](https://pubmed.ncbi.nlm.nih.gov/11273970/)
- Wang XS, Tabor MW (1988b). Studies of the reactivity of morpholine, 2-mercaptobenzothiazole and 2 of their derivatives with selected amino acids. *Contact Dermat*, 19(1):16–21. doi:[10.1111/j.1600-0536.1988.tb02862.x](https://doi.org/10.1111/j.1600-0536.1988.tb02862.x) PMID:[3180765](https://pubmed.ncbi.nlm.nih.gov/3180765/)
- Warburton KL, Urwin R, Carder M, Turner S, Agius R, Wilkinson SM (2015). UK rates of occupational skin disease attributed to rubber accelerators, 1996–2012. *Contact Dermat*, 72(5):305–11. doi:[10.1111/cod.12356](https://doi.org/10.1111/cod.12356) PMID:[25711250](https://pubmed.ncbi.nlm.nih.gov/25711250/)
- Wick A, Fink G, Ternes TA (2010). Comparison of electrospray ionization and atmospheric pressure chemical ionization for multi-residue analysis of biocides, UV-filters and benzothiazoles in aqueous matrices and activated sludge by liquid chromatography-tandem mass spectrometry. *J Chromatogr A*, 1217(14):2088–103. doi:[10.1016/j.chroma.2010.01.079](https://doi.org/10.1016/j.chroma.2010.01.079) PMID:[20202641](https://pubmed.ncbi.nlm.nih.gov/20202641/)
- Wilkinson SM, Cartwright PH, English JS (1990). Allergic contact dermatitis from mercaptobenzothiazole in a releasing fluid. *Contact Dermat*, 23(5):370. doi:[10.1111/j.1600-0536.1990.tb05175.x](https://doi.org/10.1111/j.1600-0536.1990.tb05175.x) PMID:[2151376](https://pubmed.ncbi.nlm.nih.gov/2151376/)
- Ye Y, Weiwei J, Na L, Mei M, Kaifeng R, Zijian W (2014). Application of the SOS/umu test and high-content in vitro micronucleus test to determine genotoxicity and cytotoxicity of nine benzothiazoles. *J Appl Toxicol*, 34(12):1400–8. doi:[10.1002/jat.2972](https://doi.org/10.1002/jat.2972) PMID:[24478133](https://pubmed.ncbi.nlm.nih.gov/24478133/)

