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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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2-Mercapto-benzothiazole

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2-Mercaptobenzothiazole

1 Summary and assessment

On oral administration, 2-mercaptobenzothiazole is rapidly and completely absorbed from the gastrointestinal tract. When 2-mercaptobenzothiazole is applied to the skin under occlusive cover for 96 h, about 16.1 to 17.5% is absorbed by the rat and about 33.4% by the guinea pig. On semi-occlusive application to the skin, absorption rates of about 9% for intact skin and about 37% for scarified skin are reported for guinea pigs. There are no studies available on absorption via the respiratory tract. On absorption, 2-mercaptobenzothiazole is distributed throughout the entire body. In guinea pigs, the total activity in the internal organs was highest 15 min after subcutaneous administration and then fell rapidly. The highest tissue concentrations at this time were found in the kidney, liver and lung. Excretion is largely independent of the route of administration, frequency of administration, species and sex and takes place predominantly in the urine in the metabolised form. Free 2-mercaptobenzothiazole does not appear in the urine, or occurs only in very small quantities. Metabolic transformation of 2-mercaptobenzothiazole takes place exclusively at the SH-group of the molecule. A glucuronide, a glutathione conjugate and the mercapturic acid formed from this as well as a sulphate have been detected as metabolites. Following repeated oral administration to rats of unlabelled 2-mercaptobenzothiazole followed by a single administration of radioactively labelled compound, half-lives of elimination from the plasma have been calculated to be 4.7–8.56 h and 5780–6000 h for the alpha and beta phases, respectively, and half-lives of elimination from whole blood have been found to be 3.73–4.13 h and 79.6–312 h for the alpha and beta phases, respectively. About 71–92% of the administered dose is excreted in the urine within 24 h after the last administration. Within 96 h, about 91–101% in total is found in the urine and 5–10% in the faeces. At this time, 1.57–1.95% of the administered radioactivity was detectable in the body with the highest levels in the blood and thyroid. In guinea pigs, 48 h after a single subcutaneous administration (at which time 94% of the administered dose had been excreted in the urine), the residual activity in the body was 0.19% of the administered dose and again the highest levels were observed in the blood and thyroid. A more precise analysis of the radioactivity in the blood of the rat after re-

peated oral administration has shown that 2-mercaptobenzothiazole and/or its metabolites are bound covalently to the cell membranes of the erythrocytes and are non-extractable. The relatively long half-life of the beta phase elimination of 2-mercaptobenzothiazole from plasma and whole blood may be explained by this binding, which the authors suggest is protein binding via the SH-group of 2-mercaptobenzothiazole. No significant binding to the DNA of the liver, kidneys, pituitary, pancreas or bone marrow has been found in the rat.

In the majority of the studies available, 2-mercaptobenzothiazole was found to have low toxicity on acute oral, dermal and inhalation administration (LD_{50} rat oral 2830–11804 mg/kg body weight, LD_{50} rabbit dermal > 7940 mg/kg body weight, LC_{50} rat 4 h > 1270 mg/m^3 and 7 h > 715 mg/m^3 (presumably maximum technically achievable concentrations at 50°C and 40°C)). In two isolated studies, LD_{50} values for rats have been found according to which 2-mercaptobenzothiazole is harmful on oral administration (1800 and 1680 mg/kg body weight). For mice and rabbits, oral LD_{50} values have been reported to range from 1490 to 5000 and from 7500 to 8750 mg/kg body weight, respectively.

2-Mercaptobenzothiazole does not have an irritant effect on the skin of the rabbit either on 24 h semi-occlusive application to intact or scarified skin or on 24 h occlusive application to intact skin. Instillation of 2-mercaptobenzothiazole into the rabbit eye leads to a reversible irritant effect with discharge, conjunctivitis and iritis. In the majority of studies on rabbit eyes, 2-mercaptobenzothiazole was characterised as being slightly irritant by the authors, and in one study each it was described as non-irritant and irritant to the rabbit eye.

2-Mercaptobenzothiazole produces skin sensitisation in guinea pigs in the maximisation test and in the optimisation test as well as in most patch tests. In the sensitisation tests according to OECD or EC guidelines, the chemical is used as a positive control for mild to moderately sensitising substances. 2-Mercaptobenzothiazole also shows sensitising potential in the lymph node test in the mouse.

In a 90-day oral gavage study in F344/N rats, a delay in body weight gain was seen in the females at dose levels of and above 750 mg/kg body weight per day and in the males after administration of 1500 mg/kg body

weight per day. Over the entire dose range tested from 187.5 to 1500 mg/kg body weight, the animals showed a dose-dependent increase in liver weight without any histopathological correlate. Gross pathology and histopathology did not reveal any changes in the rat after 90 days' administration of up to 1500 mg/kg body weight. In B6C3F1 mice, mortality was increased, and liver weight was increased without histopathological correlate, at the highest test dose of 1500 mg/kg body weight per day administered by gavage for 90 days. Clinical symptoms (tear flow, salivation and clonic seizures) were seen at dose levels of and above 375 mg/kg body weight. As in the rat, gross pathology and histopathology revealed no changes after 90 days' administration of up to 1500 mg/kg body weight. No clinical chemistry and/or haematology tests were performed in these preliminary studies for carcinogenicity. In S1c.ddY mice, mortality was slightly increased in both males and females on 20-month administration of 2-mercaptobenzothiazole in feed at the highest test dose of 1920 ppm in feed (about 270 mg/kg body weight per day). Furthermore, starting at 480 ppm in feed (about 60 mg/kg body weight per day), impairment of body weight gain and unspecified interstitial cell infiltration in the kidneys were found only in the males. Of the haematological parameters, only the haematocrit was reduced in the males of the top dose group. The clinical chemistry results were equivalent to those of the controls in all dose groups. In females and males, 480 ppm (approx. 60 mg/kg body weight per day) and about 120 ppm (approx. 14 mg/kg body weight per day), respectively, were without any findings.

2-Mercaptobenzothiazole displays no mutagenic activity in the Salmonella/microsome test carried out as standard plate incorporation tests or preincubation tests with the *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1537 or TA 1538 either with or without metabolic activation. The results obtained for the gene mutagenic action of 2-mercaptobenzothiazole in mammalian cells by means of the HPRT test on lung fibroblasts and Chinese hamster ovary cells (V79 and CHO cells) were negative both with and without metabolic activation. In a total of 3 tests on mouse lymphoma cells (L5178Y/TK test), which were all carried out both with and without metabolic activation, 2-mercaptobenzothiazole was evaluated as negative, as weakly mutagenic at highly toxic concentrations, and as negative in the absence but positive in the presence of metabolic activation. A chromosome-damaging effect of 2-mercaptobenzothiazole was seen in

vitro in the chromosome aberration test in Chinese hamster ovary cells (CHO) with metabolic activation. Without metabolic activation, the test was negative. In the DNA repair test in *Escherichia coli*, 2-mercaptobenzothiazole did not show any DNA-damaging activity. In studies carried out as part of the "National Toxicology Program" (NTP), 2-mercaptobenzothiazole was assessed by the authors as being positive in the SCE test in Chinese hamster ovary cells. Closer examination of the individual values presented in the tables shows, however, that in the SCE tests, which were performed in two independent laboratories, the results are doubtful and contradictory. In one study in *Saccharomyces cerevisiae* D4, 2-mercaptobenzothiazole did not induce mitotic gene conversion (induction of tryptophan-independent mutants) either with or without metabolic activation. The in vivo results of the micronucleus test in rats and mice carried out according to valid guidelines, the dominant-lethal test in rats and DNA-binding studies in rats do not provide any indication of genotoxic potential of 2-mercaptobenzothiazole. A positive result from an embryotoxicity/dominant-lethal study, which is of doubtful validity because of poor experimental conduct and documentation, has been disproved by the clear negative results of a dominant-lethal test performed according to valid test guidelines as mentioned above. The relevance of a mutagenicity test in *Drosophila melanogaster*, in which oral administration of 20–40 mg 2-mercaptobenzothiazole/ml feed over 8 to 10 days was reported to give a mutation rate of 2.5 ± 0.49%, cannot be properly assessed as the documentation of the study as a whole is unsatisfactory and, in particular, data for controls are missing. Thus, overall there are no findings which would indicate a relevant genotoxic potential of 2-mercaptobenzothiazole.

In a carcinogenicity test by the NTP, female rats were treated with 0, 188 or 375 mg 2-mercaptobenzothiazole/kg body weight daily, and male rats and male and female mice received 0, 375 and 750 mg body weight daily by oral gavage on 5 days a week for 103 weeks. Maize germ oil (corn oil) was used as the vehicle. 2-Mercaptobenzothiazole led to a statistically significant reduction in survival time in the male rats of both dose groups (375 and 750 mg/kg body weight), while in the female mice treatment-related reduction in survival time resulted only in the high dose group (750 mg/kg body weight), so that in this case the maximum tolerated dose was exceeded. In the male rats, a significant increase in the incidence of monocyte leukaemia, pituitary adenomas and pancreatic cell adenomas was described only

in the low-dose group, while in both dose groups, but more pronouncedly in the low-dose group, there was a significant increase in total benign and malignant phaeochromocytomas of the adrenal glands and in total preputial adenomas and carcinomas, compared with study controls. In comparison with historical control data, however, the incidences were not increased. No dose-dependency of the findings was seen for any of the 4 types of tumour. Furthermore, it is known that the administration of maize germ oil by gavage increases the incidence of pancreatic cell adenomas. In the female rats, increase in benign adrenal phaeochromocytomas and pituitary adenomas was statistically significant in the top dose group and exhibited a significant dose-dependent trend in comparison with study controls. Here, too, the incidence of these tumours does not, however, exceed the values for historical controls. In the female mice, the incidence of the sum of liver adenomas and liver carcinomas was increased only in the low-dose group and, hence, was clearly not dose-dependent. In comparison with historical controls, however, this incidence was also within the normal range. The tumour incidences in the male mice did not differ from those of the simultaneous controls. In summary it can be said that in the study described above, the male and female rats and the female mice showed only non-dose-dependent changes in tumour incidences of individual organs. The two species were affected by types of tumour which are known to occur spontaneously and their incidence in the exposed animals was within the range of historical control data. Moreover, systemic toxicity was observed with both of the administered doses in male rats and with the high dose in female mice, i. e. the maximum tolerated dose was exceeded. In a carcinogenicity study in S1c.ddY mice with administration of up to 1920 ppm in feed (corresponding to about 290 mg/kg body weight per day in the males and about 250 mg/kg body weight per day for the females) over a period of 20 months, no results were obtained that would indicate a carcinogenic potential for 2-mercaptobenzothiazole. Similarly, in older exploratory carcinogenicity studies in the (C57BL/6xC3H/ANF)F_1 mouse and the (C57BL/6xAKR)F_1 mouse, oral administration of 100 mg 2-mercaptobenzothiazole/kg body weight per day by gavage for 21 days and subsequently 323 ppm in the feed for 17 months (about 50 mg/kg body weight) or a single subcutaneous administration of 215 or 1000 mg/kg body weight and an 18-month observation period showed no increased incidence of tumours and no dose-dependently increased tumour incidence, respectively. Overall, careful evaluation of the available carcinogenicity studies yields no findings which

could be regarded as indicative of a carcinogenic potential of 2-mercaptobenzothiazole.

The findings in the cell transformation test in the mouse were doubtful in one study and negative in a second study.

In the context of the U.S. Toxic Substances Control Act, the reproductive toxicity potential of 2-mercaptobenzothiazole was comprehensively investigated in accordance with the U.S. Environmental Protection Agency's testing guidelines in teratogenicity/embryotoxicity studies in the rat and the rabbit, in a two-generation study in the rat as well as in a dominant-lethal test in the rat. None of the studies produced any evidence of reproductive toxicity due to 2-mercaptobenzothiazole. Only in one older study in the ICR mouse with administration of a maternally toxic dose of 1000 mg/kg body weight per day during gestation were foetal effects seen in the form of increased foetal mortality, reduced birthweight and delayed ossification. The incidences of external, skeletal and visceral malformations as well as postnatal development of the pups up to the 21st day of life were not affected by the treatment. Thus, 2-mercaptobenzothiazole has no reproductive toxicity potential at maternally nontoxic doses.

In extensive acute and subchronic neurotoxicity studies in the Sprague-Dawley rat, there were no indications of neurotoxic potential of 2-mercaptobenzothiazole from a functional observational battery, motor activity tests or neurohistopathological examination.

Older studies report that the activity of dopamine-β-hydroxylase and thus the conversion of dopamine to noradrenaline was inhibited both in vitro and in vivo by 2-mercaptobenzothiazole.

In humans, 2-mercaptobenzothiazole has a skin-sensitising effect. A skin-irritant effect has not been found in the patch test with repeated occlusive application. In an epidemiological study, an increased incidence of malignant bladder tumour disease was found in workers exposed to 2-mercaptobenzothiazole in a factory producing chemicals for the rubber industry. It cannot be ruled out, however, that these workers were also exposed to p-aminobiphenyl, which has been demonstrated to cause bladder tumours in humans (production of 2-mercaptobenzothiazole and p-aminobiphenyl since 1934 and 1935, respectively). In the study subcohort that was verifiably not exposed to p-aminobiphenyl as the workers were not employed until

after 1955 after production of the chemical had been stopped, there were no deaths from bladder cancer. The absence of urinary bladder tumours in this subcohort suggests that 2-mercaptobenzothiazole lacks urinary bladder carcinogenicity; nevertheless, based on statistical considerations (only 0.2 expected cases on the closing date of the study, 31.12.1996), it cannot be stated with certainty that 2-mercaptobenzothiazole is not a bladder carcinogen. In a second epidemiological study of workers in another factory for rubber chemicals in which 2-mercaptobenzothiazole and 2-mercaptobenzothiazole derivatives had been produced since 1932, the first vital status assessment at the closing date of the study on 31.12.1986 gave no indication of increased tumour-induced mortality due to 2-mercaptobenzothiazole exposure. A second investigation of the cohort, for which the closing date of the study was 31.12.1996, showed the incidence of urinary bladder tumour to be significantly increased in individuals exposed to 2-mercaptobenzothiazole, phenyl-β-naphthylamine, o-toluidine and/or aniline. When individual cumulative duration of employment and individual cumulative exposure (to 2-mercaptobenzothiazole only) were taken into account, it was shown that with increasing duration of employment in phenyl-β-naphthylamine production, where there was also exposure to the known bladder carcinogen β-naphthylamine, the relative risk of developing a bladder tumour increased markedly. Such a dose-response relationship was also established for workers employed in o-toluidine production, but not for workers employed in the production of aniline or 2-mercaptobenzothiazole. Therefore, the investigators suspected that the bladder tumour-inducing noxious agent was to be found not in the context of 2-mercaptobenzothiazole or aniline production, but in phenyl-β-naphthylamine or o-toluidine production.

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) has assigned 2-mercaptobenzothiazole to category 3 of carcinogenic working substances, i.e. the category of “substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data”, and to pregnancy risk group C, i.e. substances for which “there is no reason to fear a risk of damage to the embryo or foetus when MAK and BAT values are observed”. The Commission has set the MAK value (maximum workplace concentration) at 4 mg/m³ I (i. e. measured as the inhalable fraction of the aerosol) and designated the substance with “Sh” on ac-

count of its sensitising potential. The toxicology advisory council ("Beraterkreis Toxikologie") to the hazardous substances committee ("Ausschuss für Gefahrstoffe" (AGS)) has not assigned 2-mercaptobenzothiazole to any of the three carcinogenicity categories. Following adoption by the AGS of the toxicology advisory council's proposal for classification (expected in 2001), 2-mercaptobenzothiazole would not be legally classified in the Federal Republic of Germany.

2 Name of substance

2.1	Usual name	2-Mercaptobenzothiazole
2.2	IUPAC name	2-Mercaptobenzothiazole
2.3	CAS No.	149-30-4
2.4	EINECS No.	205-736-8

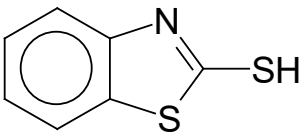
3 Synonyms, common and trade names

Accel M
Accelerator M
2-Benzothiazolethiol
Benzothiazol-2-thiol
2-Benzothiazole-2-thione
2(3H)-Benzothiazolethione
2-Benzothiazolinethione
2(3H)-Benzothiazolinethione
Benzothiazoline-2-thione
Benzothiazol-2 Mercaptan
2-Benzothiazolyl mercaptan
Captax
Dermacid
Ekagom G
Kaptaks
Kaptax
MBT
MBT WTR 23
Mebetizole

Mebithizol
Mercaptobenzenethiazole
2-Mercaptobenzothiazol
2-Mercaptobenzothiazole (ACN)
2-Mercaptobenzthiazole
Mertax
Nokuseller M
Nuodeb 84
Pennac MBT Powder
Pneumax MBT
Rotax
Royal MBT
Sulfadene
Soxinol M
Thiotax
Vulkacit M
Vulkacit Mercapto
Vulkacit Mercapto/C
Vulkacit Merkapto
Vulkacit Merkapto/C
Vulkacit Merkapto/MG
Vulkacit Merkapto/MGC

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_7H_5NS_2$

5 Physical and chemical properties

5.1 Molecular mass, g/mol 167.25

5.2	Melting point, °C	177–181 (Eastman Kodak, 1981) 180.2–181.7 (EC, 1996 a) 180.2 (Farr and Kirwin, 1994) 170.0–175.0 (technical grade product) (Windholz et al., 1983) 174–184 (Bayer, 1995 a, b, c, d) 181 (Lide and Frederikse, 1996)
5.3	Boiling point, °C	Decomposition at temperatures > 260 (at 1013 hPa) (EC, 1996 a)
5.4	Vapour pressure, hPa	< 0.000003 (at 25 °C) (EC, 1996 a)
5.5	Density, g/cm³	1.42 (at 20 °C) (Farr and Kirwin, 1994; Lide and Frederikse, 1996; EC, 1996 a) 1.42–1.5 (at 25 °C) (EC, 1996 a)
5.6	Solubility in water	< 0.1% (Eastman Kodak, 1981) 0.032 g/100 ml (at 25 °C) (Monsanto, 1987) 150 mg/l (EC, 1996 a) 51 mg/l (at pH 5) 118 mg/l (at pH 7 and 25 °C) 900 mg/l (at pH 9) (EC, 1996 a)
5.7	Solubility in organic solvents	Acetone and DMSO ≥ 10% Octanol ≥ 1% (Eastman Kodak, 1981) Acetone (10 g/100 ml) Ether (1 g/100 ml) Alcohol (2 g/100 ml) Benzene (1 g/100 ml) Tetrachloromethane (< 0.2 g/100 ml) Naphtha (< 0.5 g/100 ml) Glacial acetic acid (moderately soluble) (at 25 °C) (Windholz et al., 1983)
5.8	Solubility in fat	Corn oil ≥ 0.1% (Eastman Kodak, 1981) Partition coefficient log P_{ow}: 2.34–2.34 (measured) (EC, 1996 a)
5.9	pH value	7 (at 118 mg/l and 25 °C) (EC, 1996 a)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 6.85 mg/m³ 1 mg/m³ ≙ 0.15 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

2-Mercaptobenzothiazole is used as a vulcanisation accelerator in the rubber industry in the manufacture of tyres and technical rubber items, such as seals, tubing, footwear, rubber soles, EPDM rubber and rubber threads. It is also used in small amounts as a stabiliser in photographic emulsions (BUA, 1992).

7 Experimental results

7.1 Toxicokinetics and metabolism

The toxicokinetics and metabolism of 2-mercaptobenzothiazole have been investigated within the framework of the United States Toxic Substances Control Act in accordance with the U.S. Environmental Protection Agency's (EPA) testing guidelines (EPA, 1985 b) by conducting a series of individual oral, intravenous and dermal studies in male and female Fischer-344 rats and dermal exposure studies in female Hartley guinea pigs. As a rule, groups of 4 animals were treated per dose, sex and, where appropriate, time point of assessment and species. Administered by oral gavage as a solution in corn oil, ^{14}C-2-mercaptobenzothiazole was given as single doses of 55.5 mg (0.0497 mCi)/kg body weight or 0.592 mg (0.0590 mCi)/kg body weight, while in repeated oral dosing, unlabelled 2-mercaptobenzothiazole was given daily at 0.509 mg/kg body weight for 14 days followed by a corresponding dose (0.503 mg (0.0586 mCi)/kg body weight) of the radiolabelled substance on day 15. A single occlusive dermal application of ^{14}C-2-mercaptobenzothiazole to the depilated dorsal skin of the rat and the guinea pig was carried out with a tetrahydrofuran solution containing 36.1 µg (5.01 µCi)/animal for 96 hours, whereas a single intravenous injection of radiolabelled 2-mercaptobenzothiazole, formulated in Emulphor, tetrahydrofuran and water, was given at 0.602 mg (63.3 µCi)/kg body weight, some animals receiving only 0.519 mg (64 µCi)/kg body weight. The studies were carried out with unlabelled 2-mercaptobenzothiazole (97.6 to 100% pure) and ring-labelled ^{14}C-2-mercaptobenzothiazole with a specific activity of 29 mCi/mmol and a radiochemical purity of 95.5 to 98.6% (81 to 100% in the intravenous study). The administered 2-mercaptobenzothiazole, particularly in the intravenous study, contained different amounts of 2-mercaptobenzothiazole disulphide (MBTS, an oxidised form of 2-mercaptobenzothia-

zole), varying from < 1 to 19%. MBTS, as discussed by the investigators, is an interconversion product of 2-mercaptobenzothiazole, the formation of which is facilitated by peroxides which are always present in tetrahydrofuran, the vehicle employed. As parallel studies demonstrated that the toxicokinetics and metabolism of MBTS and 2-mercaptobenzothiazole were almost identical, the interconversion does not affect the outcome of the studies, according to the investigators' discussion of their results. Following oral and dermal administration, the amounts of radioactivity in urine, faeces, plasma and whole blood were measured at intervals, beginning 8 hours after administration, for a total period of 96 hours. Elimination in the exhaled air was not investigated. Distribution in the body following repeated oral administration was monitored over a period of 96 hours after the last dose. A more accurate qualitative analysis of the metabolites excreted in urine after repeated oral administration was carried out by HPLC subsequent to hydrolysis or enzyme treatment with β-glucuronidase and aryl sulphate sulphatase. The faeces were not analysed for metabolites. Table 1 in the appendix gives a comparative summary of the toxicokinetic data thus obtained. The urinary excretion data suggest rapid and complete absorption of 2-mercaptobenzothiazole from the gastrointestinal tract. When 2-mercaptobenzothiazole was applied to the skin under occlusive cover for 96 hours, approx. 16.1 to 17.5% was absorbed by the rat and approx. 33.4% by the guinea pig. The investigators suggested that the higher absorption rate found in the guinea pig was due to species-related factors, but they also pointed out that the area of application was larger in the guinea pigs (5 cm² compared with 2 cm² in the rats), the dose/animal being the same. In the region of the application areas, recovery of the applied radioactivity was between 51.6 and 61.5% in the rat, whereas it was 15.8% in the guinea pig. On absorption, 2-mercaptobenzothiazole was distributed throughout the entire body. Following repeated oral administration, the highest tissue concentrations were found in the kidney, thyroid gland, liver, plasma and whole blood at 8 hours after the last dose (the first time point of assessment), the male rats exhibiting slightly higher values than the female rats. The levels found in the whole blood of males after single and repeated administration of corresponding doses did not differ significantly. The females were found to have slightly lower levels in the whole blood after repeated doses than they had after a single dose, an observation which was interpreted by the investigators as possibly being indicative of slight enzyme induction after repeated dosing. The half-lives for whole blood,

which were calculated using an open two-compartment model (CSTRIP-NONLIN), exhibited no sex-specific differences or differences related to the duration of treatment. For repeated oral dosing, respective half-lives of elimination from the plasma were calculated for males and females as being 4.7 and 8.56 hours for the alpha phase and 6000 and 5780 hours for the beta phase, while the corresponding values for whole blood were 4.13 and 3.73 hours for the alpha phase and 312 and 79.6 hours for the beta phase. Excretion was largely independent of the route of administration, frequency of administration, species and sex and takes place predominantly in the urine in the metabolised form. On repeated oral dosing, as much as approx. 71% (males) and approx. 92% (females) of the administered radioactivity was excreted in urine within 24 hours, the corresponding fractions found after 96 hours being approx. 91% (males) and 101% (females). Faecal excretion, which reached a maximum between 8 and 48 hours after administration, was observed to be approx. 10 and approx. 5% of the radioactivity administered to males and females, respectively, at 96 hours after dosing. After 96 hours, fractions of 1.95% (males) and 1.57% (females) of the administered radioactivity were still detectable in the body, the highest concentrations being found in whole blood (7.35 and 9.52 nCi/ml; 1.2 and 1.53% of the administered dose (for males and females, respectively)) and in the thyroid gland (6.49 and 7.26 nCi/g; 0.001% of the administered dose (for males and females, respectively)). A more precise analysis of the radioactivity present in the blood at 24 hours after repeated oral administration showed that the predominant portion of the activity was covalently bound to the cell membranes of the erythrocytes and was non-extractable. The relatively long half-life of the beta phase elimination of 2-mercaptobenzothiazole from plasma and whole blood may be explained by this binding, which, as the investigators suggest, consists in protein binding via the SH group of 2-mercaptobenzothiazole. Metabolites identified by means of exploratory qualitative analysis of the urine collected from one animal/sex after single oral, topical and intravenous dosing revealed 2 major metabolites and small amounts of 2 to 5 additional metabolites. Following intravenous and single oral administration of the lower dose, in both cases the data from one female indicated excretion of unchanged 2-mercaptobenzothiazole. Upon repeated oral dosing, when the metabolites excreted in urine were analysed more closely, only 2 compounds were identified. One of the two metabolites was identified as the thioglucuronide. The second metabolite could not be clearly identified. It showed resistance to acid, β-glucuronida-

se and aryl sulphate sulphatase, was methylated by diazomethane and had UV spectral characteristics which indicated modification of the SH group, leading the investigators to conclude that the metabolite was oxidised at the SH group. The two metabolites were not quantified. No unchanged 2-mercaptobenzothiazole was detected in urine upon repeated oral administration. The investigators pointed out that they were not able to detect a sulphate metabolite such as that described by Nagamatsu et al. (1979; see below; El Dareer et al., 1989; SoRI, 1986 a, b, c, 1987 a, b).

The male guinea pig was used to study the absorption into, and the distribution within, the body following dermal application of ^{14}C-2-mercaptobenzothiazole (99% pure) to the intact and abraded skin as well as the distribution and metabolism following subcutaneous administration of the radiolabelled chemical. Groups of 6 animals had an area of 16 cm² of depilated intact or abraded skin treated semi-occlusively with approx. 11 mg/kg body weight ^{14}C-labelled 2-mercaptobenzothiazole. Within 48 hours, the respective fractions absorbed via the intact skin and the abraded skin were approx. 9% and approx. 37% (amounts of radioactivity excreted in urine and faeces together), while approx. 12 and 7%, respectively, of the radioactivity was detectable in the skin at the site of application and approx. 61 and 38%, respectively, of the administered activity was recovered in the material used for covering and in the skin wash (total recovery approx. 82%). Excretion took place almost entirely via the urinary route. Maximum urine concentrations were observed 3 to 6 hours after dosing. The blood, internal organs and gastrointestinal tract were found to contain respective fractions of approx. 0.12 and approx. 0.26% of the administered dose after 48 hours. The highest specific radioactivity observed at 48 hours after dosing was in the thyroid gland, followed by the blood, kidney and lung. Subcutaneous treatment of 21 male guinea pigs was carried out with a single dose of 2-^{14}C-labelled 2-mercaptobenzothiazole at 5 mg/kg body weight. At 15, 30, 60 minutes and 3, 6 and 48 hours after administration, the distribution of radioactivity in the body was measured in groups of 3 animals. Total activity peaked in the internal organs after 15 minutes and then dropped rapidly. Autoradiography of one guinea pig after 15 minutes showed the highest activity levels to be in the kidney, urinary bladder, gall bladder and lacrimal gland. Quantitative analysis revealed that at 15 minutes after administration the highest tissue concentrations were found in the kidney, liver and lung, whereas at 30 minutes and one hour they were seen in the kid-

ney, thyroid gland and liver and at 3 and 6 hours in the kidney, thyroid gland and blood. After 48 hours, the blood and the internal organs still contained 0.11% and 0.08% of the administered radioactivity, respectively, with the highest levels being detected in the thyroid gland, the liver and the kidney. Urinary excretion of administered radioactivity within 1, 6 and 48 hours was approx. 65%, approx. 93% and approx. 94%, respectively. Urinary metabolites identified after enzyme treatment with β-glucuronidase and aryl sulphate sulphatase included a glucuronide and a sulphate, which accounted for approx. 90% of the excreted radioactivity, in addition to 7.6% unchanged 2-mercaptobenzothiazole (Nagamatsu et al., 1979).

In the context of basic research work on the development of tumour seekers, whole-body autoradiography was used to study C57/Bl mice with subcutaneously implanted B16 melanoma cells at 6 hours to 4 days after intraperitoneal administration of ^{14}C-mercaptobenzothiazole (8 kBq (0.22 µCi)/g body weight). When the distribution of radioactivity was studied 6 hours after administration, the activity was preferentially seen in the liver, blood, kidney and intestinal content. Relatively high activities were also noted in the lung and in the brown fat, while activities were found to be low in the salivary glands, the thymus gland and the implanted melanomas. By 24 hours following administration, the detectable radioactivity had already decreased substantially. The distribution pattern was essentially the same as that seen after 6 hours, except that now the relative amounts of radioactivity in the bronchi, the thyroid gland and the implanted melanoma cells were much higher. At the longest survival time of 4 days after administration, a further marked decline in radioactivity was observed, though the trend towards relative accumulation in the thyroid gland and the bronchi continued. High levels were also still seen in the melanoma cells, the red pulp of the spleen, and the kidneys at 2 and 4 days after administration (Mårs and Larsson, 1995).

The 72-hour urine from 2 male Wistar rats which was collected after single oral administration of ^{35}S-2-mercaptobenzothiazole at 50 mg/animal was found to contain unchanged ^{35}S-2-mercaptobenzothiazole, ^{35}S-2-mercaptobenzothiazole sulphate, ^{35}S-2-mercaptobenzothiazole glucuronide and predominantly unlabelled benzothiazyl 2-mercapturic acid. No quantitative analysis of metabolites was carried out. The overall recovery of radioactivity in the urine and faeces was 79.4 and 1.4%, respectively. In the discussion of their results, the investigators suggested that the S atom in the SH

group of 2-mercaptobenzothiazole was replaced by endogenous sulphur from the L-cysteine pool by way of conversion of the intermediate glutathione conjugate to the corresponding cysteine conjugate, the C-S bond of which can be cleaved by cysteine conjugate β-lyase. In a later study in which 3 or 5 male Wistar rats received a single oral 2-^{14}C-mercaptobenzothiazole dose of 250 mg/kg body weight, the investigators confirmed most of their previous findings. Within 72 hours after dosing, the rats excreted 97.9% of the administered radioactivity in the urine, 1.7% in the faeces and less than 1.9% in the exhaled air. Again, the metabolites found included the sulphate, glucuronic acid and mercapturic acid derivatives, in-vitro studies in rat liver and rat kidney homogenates confirming the formation of the sulphate and glucuronide (Fukuoka and Tanaka, 1987; Fukuoka et al., 1995).

Enzymatic cleavage of the S atoms in the SH group of 2-mercaptobenzothiazole had already been suspected earlier on by Colucci and Buyske (1965), who demonstrated that the urine (collected for up to 14 days) of male rats given a single intraperitoneal injection of ^{35}S-2-mercaptobenzothiazole at 50 mg/kg body weight contained unchanged ^{35}S-2-mercaptobenzothiazole, ^{35}S-2-mercaptobenzothiazole glucuronide of slightly lower activity than the parent compound, ^{35}S-2-mercaptobenzothiazole sulphate and unlabelled benzothiazyl 2-mercapturic acid. The metabolites were not quantified (Colucci and Buyske, 1965).

Bakke et al. (1989), after finding increased methanesulphinic acid excretion in the 24-hour urine of male Sprague-Dawley rats given a single oral dose of ^{35}S-2-mercaptobenzothiazole of 5 mg/animal, postulated that the SH group of 2-mercaptobenzothiazole underwent methylation. The next suggested step after methylation and subsequent oxidation consists in the displacement of unstable CH_3SO^-, which in turn decomposes or is metabolised to carbon dioxide and the sulphate anion or oxidised to the methanesulphinate ion ($CH_3SO_2^-$). The investigators further suggested that the remaining benzothiazole molecule forms a conjugate with glutathione which could in turn yield the initial 2-mercaptobenzothiazole. As with the metabolic pathway proposed by Fukuoka and Tanaka (1987), this type of conversion would result in the sulphur atom of the SH group of 2-mercaptobenzothiazole being exchanged for endogenous sulphur (Bakke et al., 1989).

The toxicokinetics of 2-mercaptobenzothiazole in rats after single oral administration of 10 to 50% of the LD_{50} (LD_{50} given as 11804 mg/kg body

weight) or single 4-hour exposure to 2-mercaptobenzothiazole concentrations of 90 to 530 mg/m³ was also investigated in the former Soviet Union. These studies also demonstrated rapid absorption, distribution and renal excretion (Datsenko and Korneychuk, 1991, 1993). However, the investigators started from the false premise that 2-mercaptobenzothiazole is not metabolised in the body (though in fact almost complete metabolisation takes place at the SH group, see above), and it remains unclear whether the analytical method they employed (polarographic determination with a dropping mercury electrode after conversion to the nitro derivative) detected both unchanged 2-mercaptobenzothiazole and its metabolites. Therefore, the toxicokinetic parameters calculated by these investigators is not given here.

In vitro, methylation of the SH group of 2-mercaptobenzothiazole by thiol-S-methyltransferase, isolated from various tissues of the rat, was demonstrated in earlier studies (Kloog et al., 1982; Weisiger and Jackoby, 1979).

2-Mercaptobenzothiazole was not found to bind significantly to DNA in male and female Fischer-344 rats. Eight hours after a single administration by oral gavage of 2-mercaptobenzothiazole (2-mercapto[2-^{14}C]benzothiazole, specific activity 56 mCi/mmol, radiochemical purity 99.7%, and unlabelled 2-mercaptobenzothiazole > 98% pure) at 375 mg/kg body weight (approx. 15 mCi/kg body weight), DNA was extracted from the liver, adrenal glands, pituitary gland, pancreas and bone marrow and the covalent binding indices (CBI) were determined (a CBI of 1 = 1 DNA adduct per 10^6 nucleotides after administration of 1 mmol/kg body weight). The liver contained 0.51% (males) and 0.36% (females) of the administered activity at 8 hours after dosing, while the pancreas, adrenal glands, pituitary gland and bone marrow together contained a maximum of 0.03%. The CBI values for liver DNA ranged from 1.15 to 3.11 (males) and 0.89 to 2.02 (females; ranges were obtained with three purification methods used in parallel: exhaustive solvent extraction, caesium chloride ultracentrifugation and hydroxyapatite chromatography). Bone marrow DNA was found to have CBI values of 0.77 (males) and 0.16 (females) whilst DNA binding in the adrenal glands, pituitary gland and pancreas were below the detection limit. For comparison, the liver CBI values for 2-mercaptobenzothiazole were stated to be similar to those obtained for 3-methylcholanthrene, aniline, oestrone and diethylstilboestrol while the CBI values for potent hepatocarcinogens, such as dimethylnitrosamine and aflatoxin, were given as ranging from 6000 to > 20000 (Brewster et al., 1989 a, b; Monsanto, 1989).

7.2 Acute and subacute toxicity

Acute toxicity

The results of the studies investigating the acute toxicity of 2-mercaptobenzothiazole following oral, dermal and intraperitoneal administration and inhalation exposure are compiled in Table 2 in the appendix.

According to most studies conducted in the rat, 2-mercaptobenzothiazole was of low acute toxicity when administered orally (LD_{50} rat oral 2830 to 11804 mg/kg body weight, see Table 2). Two of the numerous studies report LD_{50} values for the rat, based on which 2-mercaptobenzothiazole is harmful upon oral administration (LD_{50} rat oral 1800 and 1680 mg/kg body weight, depending on the source of information; Uniroyal, 1975; Kowalski and Bassendowska, 1965). For mice and rabbits, oral LD_{50} values have been reported to range from 1490 to 5000 and from 7500 to 8750 mg/kg body weight, respectively (see Table 2). In acute dermal toxicity studies in rabbits and acute inhalation toxicity studies in the rat, 2-mercaptobenzothiazole was of low toxicity (LD_{50} rabbit dermal > 7940 mg/kg body weight; LC_{50} rat, > 1270 mg/m³ and > 715 mg/m³ at 4 and 7 hours, respectively (presumably representing maximum concentrations technically attainable at 50 and 40 °C); Younger Laboratories, 1974, 1975; Industrial Bio-Test, 1977 b; Dow, 1961). On intraperitoneal administration, LD_{50} values determined in rats were 150 to 400 mg/kg body weight, while in mice they were 200 to 669 mg/kg body weight. Reduced food consumption, humpback behaviour, peripheral vasodilation, lacrimation and salivation, rough coat, weakness, reduced activity, lying on the abdomen, collapse, ataxia, altered breathing (irregular breathing, increased respiratory rate, dyspnoea), convulsions and tremors, inter alia, were reported as the clinical signs of intoxication. Necropsy upon oral administration of lethal doses was without findings or revealed hyperaemia and haemorrhage of the lung, hyperaemia of the liver, pale livers with discoloured areas, kidney changes which were not further characterised, swollen small intestine and gastrointestinal inflammation. Terminal necropsy of the survivors was, as a rule, without findings (see Table 2) or, following 7-hour inhalation exposure to approx. 715 mg/m³, revealed liver and kidney changes which were not further characterised (Dow, 1961).

Subacute toxicity

The studies on the subacute toxicity of 2-mercaptobenzothiazole are summarised in Table 3 in the appendix.

The only finding from a 4-week study in which 2-mercaptobenzothiazole was administered orally in the feed of Sprague-Dawley rats consisted in retardation of body weight gain in association with reduced food consumption. The administered doses ranged from 5000 to 25000 ppm in the feed (approx. 357 to 1768 mg/kg body weight/day). Retardation of body weight gain was observed in males and females in the dose ranges ≥ 15000 ppm (approx. 1071 mg/kg body weight/day) and ≥ 20000 ppm (approx. 1429 mg/kg body weight/day), respectively (Monsanto, year not given). The exact scope of investigation is unknown, as the study is accessible only as a citation in the secondary literature (EC, 1996 a).

In preliminary studies (12 oral doses given by gavage over a period of 16 days) to a carcinogenicity study carried out in F344/N rats and B6C3F1 mice as part of the U.S. National Toxicology Program (NTP), the rats only showed depressed body weight gain at the highest test dose of 2500 mg/kg body weight. In the mouse study, the 750 mg/kg body weight dose was without remarkable findings. Starting at the next higher dose level of 1500 mg/kg body weight, the animals exhibited lethargy and prostration. Following administration of 1500 mg/kg body weight, 4 out of 5 females died, while at the highest test dose of 3000 mg/kg body weight all females and 4 out of 5 males died. Macroscopic examination of both rats and mice from all dose groups was without findings. No histology, clinical chemistry or haematology tests were carried out (NTP, 1988).

In rats, dust inhalation of 2-mercaptobenzothiazole at 350 to 400 mg/m³ air for 2 hours/day over a period of 15 days reportedly caused reduction in body weight in addition to thickening of the interalveolar septa which the investigators considered insignificant. Oxygen consumption was not increased, and the neurophysiological measurements (rheobase and chronaxy of the extensors of the hind legs) gave no indications of changes in the nervous system (no further details; Vorob'eva and Mezentseva, 1962).

In the mouse, an older study with 1-week intraperitoneal administration of 2-mercaptobenzothiazole at 110 mg/kg body weight/day describes prolongation of hexobarbital sleeping time and histopathological changes in the

kidney and liver, but not in the lung, heart, thyroid gland or testis. Administration of 55 mg/kg body weight/day was without findings (no further details; Guess and O'Leary, 1969).

7.3 Skin and mucous membrane effects

The skin irritancy studies carried out with 2-mercaptobenzothiazole are summarised in Table 4 in the appendix. 2-Mercaptobenzothiazole was not observed to cause skin irritation in the rabbit, neither after 24-hour semi-occlusive application to the intact or scarified skin nor after 24-hour occlusive application to the intact skin (Arthur D. Little Inc., 1977; Randall and Bannister, 1990; Younger Laboratories, 1974, 1975). Repeated application and intradermal injection have been reported to cause mild reversible irritation in the rabbit (Dow, 1961; Guess and O'Leary, 1969). Application of 2-mercaptobenzothiazole to the injured skin of rabbits had no inhibitory effect on healing (Guess and O'Leary, 1969). In the guinea pig, application of a watery paste was without findings (Du Pont, 1948). Application of a 10-percent formulation in acetone and corn oil, occlusive application and repeated application resulted in mild irritation in the guinea pig (Eastman Kodak, 1956, 1979, 1980).

Instillation of 2-mercaptobenzothiazole into the rabbit eye led to reversible irritant effects with discharge, conjunctivitis and iritis in the majority of studies conducted (see Table 5 in the appendix). Only one study reported reversible corneal alterations, and these were only seen in 1 out of 3 animals (Industrial Bio-Test, 1977 d). In one study, the investigators evaluated 2-mercaptobenzothiazole as not irritating in accordance with the Federal Hazardous Substances Act, 21 CFR, § 191.12 (1964; irritation index 1.3/110; Younger Laboratories, 1974). In a later study from the same laboratory, the chemical was evaluated as practically nonirritating or, applying the afore-mentioned regulation, as slightly irritating (irritation index 3.2/110; Younger Laboratories, 1975; Randall and Bannister, 1990). Evaluation as a mild eye irritant also resulted from further studies, one of which ascertained a further irritation index (18.3/110; Industrial Bio-Test, 1977 d; Dow, 1961; Eastman Kodak, 1979, 1980). In one study describing that 2-mercaptobenzothiazole instillation caused reversible iritis in 4 out of 4 rabbits and conjunctivitis that was reversible in 2 out of 4 animals during the 7-day observation period but was not reversible in the other 2 (score 1 according to

Draize), the investigators evaluated 2-mercaptobenzothiazole as irritating to the eye (Arthur D. Little Inc., 1977).

7.4 Sensitisation

The numerous animal studies on the skin-sensitising potential of 2-mercaptobenzothiazole are summarised in Table 6 in the appendix. 2-Mercaptobenzothiazole produced skin sensitisation in the guinea pig in both the Magnusson and Kligman maximisation test, the optimisation test and most patch tests. In test systems which employ only one single intradermal induction step with or without simultaneous injection of Freund's adjuvant (Single Injection Adjuvant Test, modified Draize test), 2-mercaptobenzothiazole displayed no skin-sensitising effect (Goodwin et al., 1981). The results obtained in the Landsteiner-Draize test with repeated intradermal induction in the absence of Freund's adjuvant are contradictory (Cannon Laboratories, 1977; Magnusson and Kligman, 1969). Positive sensitisation results were also obtained in lymph node assays in the mouse (local lymph node assay and popliteal lymph node assay; see Table 6). OECD guideline No. 406 and EC Directive 96/54/EC mention 2-mercaptobenzothiazole as a mild-to-moderately sensitising positive control substance for sensitisation studies in the guinea pig (EC, 1996 b; OECD, 1992).

Based on in-vitro studies, the hypothesis has been proposed that the biochemical basis for the sensitising potential of 2-mercaptobenzothiazole is the reaction of the molecule's SH group with free COOH, NH_2 and SH groups of amino acids or proteins (Wang and Tabor, 1984, 1988).

7.5 Subchronic and chronic toxicity

In a dose-finding study for a carcinogenicity study carried out as part of the U.S. NTP (see Section 7.7), groups of 10 F344/N rats and 10 B6C3F1 mice/dose and sex were given 2-mercaptobenzothiazole (as the commercial product Captax, 96.3% pure) orally at dose levels of 0, 187.5, 375, 750 and 1500 mg/kg body weight (rats) and 0, 94, 188, 375, 750 and 1500 mg/kg body weight (mice) on 5 days/week for 13 weeks. 2-Mercaptobenzothiazole was administered by oral gavage as a formulation in corn oil, the mice and rats being dosed with volumes of 10 and 5 ml/kg body weight, respectively. All animals were examined macroscopically. Histopathological examination

was performed in all animals of the control groups and the two top dose groups and in a few animals of the lower dose groups. No clinical chemistry or haematology studies were carried out. In the rats, mortality and clinical picture were comparable with the control at all dose levels; a total of 3 males and 3 females from different dose groups, however, died due to gavage errors. Markedly depressed body weight gain as compared with the controls was observed in the females of the two highest dose groups and the males of the top dose group. The relative liver weights in all dose groups were dose-dependently increased without any histopathological correlate, as were the absolute liver weights in the females of all dose groups and the males of the two highest dose groups. Macroscopic and histopathological examinations were without substance-related findings at all dose levels. The mice exhibited markedly increased mortality at the highest dose level. In the course of the study, 5 out of 10 males and 7 out of 10 females from this dose group died, one of the females succumbing to gavage error. At the 750 mg dose level, 2 out of 10 females died, one of them due to dosage error. Body weight development in all dose groups corresponded to the development seen in the controls. Dose-dependent clinical symptoms were observed in the form of lethargy, lacrimation, salivation and clonic seizures at dose levels of and above 375 mg/kg body weight. In the absence of a histopathological correlate, relative liver weights were significantly increased in the males and females of the top dose group receiving 1500 mg/kg body weight. As in the rats, macroscopic and histological examination revealed no compound-related findings in the mice at any dose level. Note: An original rat study in which 2-mercaptobenzothiazole was administered at dose levels of 0, 187.5, 375, 750, 1500 and 3000 mg/kg body weight, formulated in corn oil, dose volume 10 ml/kg body weight, was discontinued after approx. 8 weeks without statement of reasons. The animals of the 3000 mg/kg dose group all died on the second day of the study. Macroscopic and histopathological examination of these animals revealed necrotic lesions of the distal renal tubules. Epithelial changes (sloughing) in the seminal vesicles seen in the males were evaluated by the investigators as questionably treatment-related, as it was not possible to preclude that the lesions were artefacts of autolytic change (NTP, 1988; Physiological Research Laboratories, 1981).

Carcinogenicity studies, including non-neoplastic changes, in rats and mice receiving chronic 2-mercaptobenzothiazole treatment are extensively discussed in Section 7.7.

When rabbits were given 2-mercaptobenzothiazole at 20 mg/kg body weight orally every other day for a period of 2 months and then daily for 1.5 months, histological examination revealed liver alterations in the form of granular changes of the cytoplasm, round cell infiltration and indistinct hepatocellular borders. In order to assess liver function, the protein composition of the blood was analysed by means of a procedure described by the investigators as the thymol turbidity and copper acetate tests in addition to determining the aldolase and bilirubin levels in blood serum. The results of these investigations were negative, as were the haematology and macroscopic findings (no further details; Vorob'eva and Mezentseva, 1962). Insufficient documentation of the conduct and the results of the study renders it unsuitable for the assessment of the systemic toxicity of 2-mercaptobenzothiazole following repeated oral administration.

7.6 Genotoxicity

7.6.1 In vitro

The available data on the in-vitro genotoxicity of 2-mercaptobenzothiazole are summarised in Table 7 in the appendix.

Tests for mutagenic activity

The mutagenic effects of 2-mercaptobenzothiazole on procaryotes was studied in numerous Salmonella/microsome assays, which were carried out as standard plate incorporation or preincubation tests. Results are available for *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1537 and TA 1538 (see Table 7 in the appendix). 2-Mercaptobenzothiazole was mutagenic neither in the presence nor in the absence of metabolic activation. Only one study report gave an equivocal result inasmuch as a test on strain TA 98 was negative in the presence of metabolic activation in one of two laboratories, while in the second laboratory two sets of 3 separate trials, one set performed with rat liver S9 mix, the other with hamster liver S9 mix, each produced one weakly positive, one equivocal and one negati-

ve result (NTP, 1988; Zeiger et al., 1987, 1990; Zeiger, 1990). One assay without metabolic activation that was carried out in *Escherichia coli* SD-4-73 to test for induction of streptomycin-independent revertants was negative (Szybalski, 1958).

When the mutagenic potential of 2-mercaptobenzothiazole was studied in mammalian cells by means of the HPRT test on lung fibroblasts and Chinese hamster ovary cells (V79 and CHO cells), the results were negative both with and without metabolic activation (Donner et al., 1983; Pharmakon Research, 1984 b). Assays on mouse lymphoma cells (L5178Y), all of which were performed both with and without metabolic activation, gave no consistent findings. A study in L5178Y cells showed a slight increase in mutant frequency by a factor of maximum 3.1 at some very toxic concentrations; however, this result was not reproducible in any of the 4 separate assays. Overall, 2-mercaptobenzothiazole was evaluated as nonmutagenic in the L5178Y/TK assay (Litton Bionetics, 1979). 2-Mercaptobenzothiazole was evaluated as a weak mutagen at highly toxic concentration levels in a further L5178Y/TK assay, in which mutant frequencies were higher than controls by factors ranging from 1.8 to 8.7 in concentration ranges with relative growth rates of < 10% in the absence of metabolic activation, and by factors of 1.7 to 2.7 in concentration ranges with relative growth rates between 7 and 20% in the presence of metabolic activation (Litton Bionetics, 1985). An L5178Y/TK assay which was carried out as part of the U.S. NTP was negative in the absence of metabolic activation but evaluated as positive in the presence of metabolic activation, with mutant frequency in the presence of metabolic activation showing moderately reproducible and dose-dependent 1.6-fold to maximum 3-fold increases over controls at concentration levels with relative growth rates between 12 and 85% (Myhr et al., 1990; NTP, 1988; Zeiger et al., 1990; see Table 7).

Tests for chromosome-damaging activity

A chromosome-damaging effect of 2-mercaptobenzothiazole was seen in vitro in the chromosome aberration test in Chinese hamster ovary (CHO) cells with metabolic activation. Without metabolic activation, the test was negative (Anderson et al., 1990; NTP, 1988; Zeiger et al., 1990).

Tests for DNA-damaging activity and activity in indicator tests

In the DNA repair test in *Escherichia coli*, 2-mercaptobenzothiazole was not observed to have any DNA-damaging activity (Ebringer et al., 1985).

In the context of the U.S. NTP, 2-mercaptobenzothiazole was tested at two independent laboratories for its effects on SCE in CHO cells. Overall, the investigators evaluated the chemical as positive in this test system. On closer inspection, however, the two laboratories' individual results, presented in tabular format, appear to be contradictory and equivocal (Anderson et al., 1990; NTP, 1988; Zeiger et al., 1990; see Table 7). The SCE rates upon which the investigators based their positive evaluation were only 21 to 35% higher than controls, these increases being observed in cytotoxic concentration ranges and/or under experimental conditions capable of causing substance-unrelated induction of higher SCE rates (longer harvest time and hence longer bromodeoxyuridine exposure). Moreover, the increases in SCE rates evaluated as significant were neither clearly dose-dependent nor reproducible in the majority of individual tests (see Table 7). Recent suggestions regarding the evaluation of SCE tests advocate using an SCE rate increase by a factor of at least 2 over controls, the existence of a concentration-activity relationship and reproducibility of the results as criteria for determination of unequivocally positive findings (cf. Speit, 1993).

Other tests

In one study in *Saccharomyces cerevisiae* D4, 2-mercaptobenzothiazole did not induce mitotic gene conversion (induction of tryptophan-independent mutants; Litton Bionetics, 1976) either with or without metabolic activation. One study on the genotoxic effect of 2-mercaptobenzothiazole on *Euglena gracilis* was negative (Ebringer et al., 1985).

7.6.2 In vivo

The in-vivo genotoxicity tests – micronucleus tests in rats and mice, the dominant-lethal test in the rat and a DNA binding study in the rat – described in the following gave no indications that 2-mercaptobenzothiazole has a genotoxic potential.

In a micronucleus test conducted in the CD-1 mouse, 2-mercaptobenzothiazole was not mutagenic. Groups of 4 males and 4 females received 2-mercaptobenzothiazole (98.1% pure) at 300 mg/kg body weight by intraperitoneal injection as a single dose or two doses at an interval of 24 hours. The positive control was treated with triethylenemelamine, while the negative control received the vehicle, corn oil. Preparation of the bone marrow was carried out 30 and 48 hours after the single dose, and 24 and 48 hours after the second dose. At none of the time points of investigation was the frequency of micronuclei increased. The administered dose was based on the results of a preliminary study in which administration of 500 mg/kg body weight was lethal. In the main study, the animals exhibited prostration, hypoactivity, ptosis, tremor and loss of righting reflex even after a single dose of 300 mg/kg body weight (Pharmakon Research, 1984 c).

When micronucleus tests were carried out with 3 intraperitoneal doses of up to 2500 mg/kg body weight in the male B6C3F1 mouse and the male Fischer-344 rat as part of the U.S. NTP, 2-mercaptobenzothiazole was devoid of mutagenicity (no further details; NTP, 1995, 1998).

A dominant-lethal test which was carried out in the rat according to valid guidelines also gave no indication that 2-mercaptobenzothiazole possesses chromosome-damaging potential (see Section 7.8; Rodwell et al., 1991; Springborn Laboratories, 1989 e).

A positive result from an embryotoxicity/dominant-lethal study, which is of doubtful validity because of poor experimental conduct and documentation (Aleksandrov, 1982), has been disproved by the clear negative results of a dominant-lethal test performed according to valid test guidelines as mentioned above.

No significant binding of 2-mercaptobenzothiazole to the DNA of the liver, adrenal glands, pituitary gland, pancreas or bone marrow was found in the rat (see Section 7.1; Brewster et al., 1989 a, b; Monsanto, 1989).

In a mutagenicity test on *Drosophila melanogaster*, 2-mercaptobenzothiazole was administered in the feed at concentration levels of 20 to 40 mg/ml for 8 to 10 days. The mutation frequency was reported as 2.5 $\pm$ 0.49%, and the chemical was evaluated as a moderate mutagen (Revazova, 1968). As the documentation of the study is, all in all, unsatisfactory and, in particular,

data for the controls are lacking, the relevance of this finding can not be properly assessed.

7.7 Carcinogenicity

Long-term carcinogenicity studies

In a carcinogenicity study which was conducted as part of the U.S. NTP, groups of 50 male and 50 female F344/N rats and 50 male and 50 female B6C3F1 mice were given 2-mercaptobenzothiazole (as the commercial product Captax, 96 to 97% pure), formulated in corn oil, by oral gavage on 5 days/week for 103 weeks. The female rats were treated at dose levels of 0, 188 and 375 mg/kg body weight/day, while the male rats and the male and female mice were given 0, 375 or 750 mg/kg body weight/day. End-points of investigation included clinical signs, survival rates, body weight and macroscopic and histopathological findings. No haematology or clinical chemistry studies were carried out. The tumour incidences were analysed with the aid of different statistical methods (Life Table Analysis, Incidental Tumour Analysis, Cochran-Armitage linear trend test and Fisher exact test). A treatment-related, significant ($p < 0.001$) reduction was seen in the survival rates of the male rats at both nonzero dose levels starting at study weeks 85 and 83 in the low and high dose groups, respectively (mortality was seen in the control, low and high dose groups from study weeks 92, 78 and 58, respectively). Mortality among female rats did not differ significantly from the controls. Body weight gain of male rats treated with 2-mercapto-benzothiazole was comparable with controls or was higher than controls towards the end of the study. The female rats of both treatment groups showed consistently increased mean body weights relative to controls from approx. study week 7 (with a maximum of 11% seen in the top dose group at the end of the study). Following administration, the rats repeatedly exhibited lethargy and prostration. Non-neoplastic macroscopic and histopathological changes found in rats, including controls, were present in all male rats and 76 to 84% of female rats and consisted in nephropathy, characterised by tubular degeneration and regeneration, the severity of the nephropathies being evaluated as mild to moderate in the male controls and as moderate to severe in the male rats treated with 2-mercaptobenzothiazole. The biological significance of these findings was later evaluated as questio-

nable, as the severity of nephropathy was not dose-related (TSCA, 1991–93). Additional non-neoplastic changes observed in some female rats and, at a higher incidence, in the male rats of all dose groups included ulceration and irritation of the forestomach with epithelial hyperplasia and hyperkeratosis, which later were interpreted as being treatment-related (bolus effect), but not compound-related (TSCA, 1991–93). The numbers of animals with neoplastic changes, total numbers of tumours and tumour latent periods are given in Table 8, below. The number of animals that developed tumours was not, or not in a dose-related manner, affected by the administration of 2-mercaptobenzothiazole. This was also observed for the total number of tumours. While the female rats showed a dose-related increase in tumour latent period, in male rats both benign and malignant tumours dose-relatedly occurred earlier than in the control group. According to the investigators' summary of the tumour findings, the incidences of mononuclear cell leukaemia, pituitary gland adenomas and pancreatic acinar cell adenomas in male rats were found to be significantly increased ($p < 0.01$) only in the low dose group, and thus clearly were not dose-related. In the male rats of the low and high dose groups, significantly increased incidences were additionally found for benign as well as total benign or malignant (combined) adrenal gland phaeochromocytomas and total benign or malignant preputial gland adenomas or carcinomas (combined), though this was more pronounced in the low dose group than in the high dose group, and so there was no dose-relatedness. In the female rats of the high dose group, incidences of pituitary gland adenomas and benign adrenal gland phaeochromocytomas were significantly increased relative to vehicle controls ($p \leq 0.05$) with a significant dose-related trend ($p < 0.05$). All tumour incidences were within the range of the historical control data (ranges are given in Table 8) and the changes in tumour incidences were not dose-related, except for a trend which was discernible in the benign pituitary gland adenomas and the adrenal gland phaeochromocytomas in female rats. Furthermore, it is known that the administration of plain corn oil by gavage can increase the incidence of pancreatic acinar cell adenomas (Haseman et al., 1990; NTP, 1994).

Beginning of Table 8

Table 8. Mortality and tumour incidences relative to the number of F344/N rats examined following administration of 2-mercaptobenzothiazole by oral gavage on 5 days/week for 103 weeks (based on NTP, 1988)

		Study control (corn oil)	188 mg/kg b.w./day	375 mg/kg b.w./day	750 mg/kg b.w./day	Historical controls (corn oil, mean value)	Historical controls (corn oil, range)
Mortality	♂ ♀	8/50 22/50*	– 19/50*	28/50 25/50	30/50* –	no data no data	no data no data
Mononuclear cell leukaemia	♂ ♀	7/50 (14%) 6/50 (12%)	– 14/50 (28%)	16/50 (32%) 9/50 (18%)	3/50 (6%) –	14 ± 8% 19 ± 9%	2–28%[1)] 4–42%
Pancreatic acinar cell adenomas	♂ ♀	2/50 (4%) no data	– no data	13/50 (26%) no data	6/49 (12%) –	6 ± 8% no data	0–28% no data
Pituitary gland adenomas	♂ ♀	14/50 (28%) 15/49 (31%)	– 24/50 (48%)	21/50 (42%) 25/50 (50%)	12/48 (25%) –	24 ± 8% 37 ± 8%	10–38%[2)] 18–55%
Pituitary gland adenocarcinomas	♂ ♀	no data 1/49 (2%)	– 0/50 (0%)	no data 0/50 (0%)	no data –	2 ± 2% 3 ± 3%	0–9% 0–11%
Pituitary gland adenomas or adenocarcinomas, combined	♂ ♀	no data 16/49 (33%)	– 24/50 (48%)	no data 25/50 (50%)	no data –	26 ± 8% 40 ± 8%	12–44% 22–61%
Benign phaeochromocytomas of the adrenal gland	♂ ♀	18/50 (36%) 1/50 (2%)	– 5/50 (10%)	25/50 (50%) 6/50 (12%)	22/49 (45%) –	23 ± 9% 6 ± 4%	4–41% 0–14%
Malignant phaeochromocytomas of the adrenal gland	♂ ♀	0/50 (0%) no data	– no data	2/50 (4%) no data	2/49 (4%) –	1 ± 1% 0 ± 1%	0–4% 0–2%
Benign or malignant phaeochromocytomas of the adrenal gland, combined	♂ ♀	18/50 (36%) no data	– no data	27/50 (54%) no data	24/49 (49%) –	24 ± 9% 6 ± 4%	4–41%[3)] 2–16%
Preputial gland adenomas	♂	0/50 (0%)	–	4/50 (8%)	4/50 (8%)	2 ± 3%	0–14%
Preputial gland carcinomas	♂	1/50 (2%)	–	2/50 (4%)	1/50 (2%)	2 ± 3%	0–10%
Preputial gland adenomas or carcinomas, combined	♂	1/50 (2%)	–	6/50 (12%)	5/50 (10%)	4 ± 4%	0–18%
Total number of animals with (total numbers of):							
Benign tumours	♂ ♀	49/50 (100) 31/50 (55)	– 41/50 (78)	50/50 (131) 36/50 (64)	48/50 (107) –	no data no data	no data no data
Malignant tumours	♂ ♀	19/50 (20) 14/50 (17)	– 21/50 (26)	27/50 (35) 13/50 (15)	15/50 (16) –	no data no data	no data no data
Benign or malignant tumours, combined	♂ ♀	49/50 37/50	– 46/50	50/50 40/50	48/50 –	no data no data	no data no data
Tumour latent period (weeks):							
Benign tumours	♂	90		77	56		

Table 8. Mortality and tumour incidences relative to the number of F344/N rats examined following administration of 2-mercaptobenzothiazole by oral gavage on 5 days/week for 103 weeks (based on NTP, 1988)

		Study control (corn oil)	188 mg/kg b.w./day	375 mg/kg b.w./day	750 mg/kg b.w./day	Historical controls (corn oil, mean value)	Historical controls (corn oil, range)
	♀	62	66	63			
Malignant tumours	♂ ♀	90 50	 56	77 78	56		
Benign or malignant tumours, combined	♂ ♀	90 50	 56	77 63	56		

b.w. body weight
– dose not tested
* one accidental death (probably due to gavage error)
[1], [2] and [3] for more up-to-date figures from NTP carcinogenicity studies conducted between 1977 and 1987, see Haseman et al. (1990)
[1]: 2–44%
[2]: 10–54%
[3]: 4–66%

End of Table 8

Survival rate in high dose female mice was significantly reduced from study week 27 onwards, compared with controls. Mortality in the two treatment groups of male mice and in low dose female mice was comparable with controls. Male mice of both treatment groups were observed to have reduced body weight gain between study weeks 3 and 64, with recovery thereafter. Mean body weight in the high dose female mice dropped below that seen in the controls by at most 6% during the study but was back in the control range at the end of the study. At the low dose level, mean body weights observed during the study were comparable with controls or were repeatedly found to be higher than these, particularly at the end of the study. As seen in rats, mice repeatedly exhibited lethargy and prostration after dosing. Mice showed no significant, non-neoplastic pathological or histopathological lesions. Incidences of neoplastic changes are given in Table 9, below. Only in the low dose female mice was the incidence of total hepatocellular adenomas or carcinomas (combined) significant ($p = 0.028$) relative to controls, and hence this finding was clearly not dose-related. Moreover, the incidence was in the range of the historical control data (cf. Table 9). In the discussion of their results, the investigators suggested that possibly the development of hepatocellular adenomas and carcinomas in the high dose

group of female mice was prevented by reduced survival rate seen in that group, since hepatocellular neoplasms are late-appearing tumour types in mice. Significant and dose-related reductions were observed in the incidences of pituitary gland adenomas, of total benign or malignant pituitary gland tumours (combined) and of malignant lymphomas. The tumour incidences in male mice treated with 2-mercaptobenzothiazole did not differ significantly from those in the controls.

Table 9. Mortality and tumour incidences relative to the number of B6C3F1 mice examined following administration of 2-mercaptobenzothiazole by oral gavage on 5 days/week for 103 weeks (based on NTP, 1988)

		Study control (corn oil)	375 mg/kg b.w./day	750 mg/kg b.w./day	Historical controls (corn oil, mean value)	Historical controls (corn oil, range)
Mortality	♂ ♀	11/50 13/50	17/50 10/50	20/50* 28/50*	no data no data	no data no data
Hepatocellular adenomas	♂ ♀	no data 3/50 (6%)	no data 7/49 (14%)	no data 4/50 (8%)	no data 5 ± 4%	no data 0–18%
Hepatocellular carcinomas	♂ ♀	no data 1/50 (2%)	no data 5/49 (10%)	no data 0/50 (0%)	no data 3 ± 3%	no data 0–10%
Hepatocellular adenomas or carcinomas, combined	♂ ♀	16/49 (33%) 4/50 (8%)	21/50 (42%) 12/49 (24%)	14/50 (28%) 4/50 (8%)	no data 8 ± 6%	no data 0–28%
Number of animals with:						
Benign tumours	♂ ♀	20/49 25/50	24/50 21/49	16/50 11/50	no data no data	no data no data
Malignant tumours	♂ ♀	20/49 27/50	21/50 18/49	14/50 9/50	no data no data	no data no data
Benign or malignant tumours, combined	♂ ♀	31/49 38/50	39/50 33/49	25/50 15/50	no data no data	no data no data

b.w. body weight
* of the high dose mice, 6 males and 4 females died in study week 13 due to gavage error and were not included in the statistical analysis of survival rates

On the basis of the tumour incidences in male and female rats given above, the investigators concluded that there was some evidence of carcinogenic activity of 2-mercaptobenzothiazole, while for male and female mice they considered that there was no evidence and equivocal evidence, respectively (NTP, 1988). In summary it can be said that in the study described above, male and female rats and female mice showed only non-dose-re-

lated changes in some tumour incidences. Moreover, the tumour types in question occur spontaneously and their incidences were all in the range of the historical control data. Moreover, systemic toxicity was observed with both administered doses in male rats and with the high dose in female mice.

In a further long-term carcinogenicity study in Slc:ddY mice, no results were obtained which would have indicated a carcinogenic potential for 2-mercaptobenzothiazole. The commercial product Nokuseller M (technical grade, no precise details of purity given), was administered in feed to groups of 30 males and 30 females at concentration levels of 30, 120, 480 and 1920 ppm for 20 months. Based on feed consumption, this corresponded to a daily 2-mercaptobenzothiazole intake of 3.60, 14.69, 57.90 and 289.40 mg/kg body in males and 3.61, 13.52, 58.87 and 247.98 mg/kg body weight in females. Groups of 60 animals/sex served as controls. After 6 and 12 months, interim necropsies were performed on 5 animals from each dose group and 10 animals from the control group. At the interim necropsies and at study termination, comprehensive haematology and clinical chemistry studies were carried out in addition to macroscopic examination and weight determination of the brain, heart, lung, liver, kidney, spleen and testis as well as macroscopic examination without weight determination of the pituitary gland, thyroid gland, maxillary gland, stomach, small intestine, pancreas, ovaries, uterus, epididymis, seminal vesicle, urinary bladder, muscles, sciatic nerve, sternum, femoral bone and spinal cord. Histological studies were performed on the lung, liver, kidney and haematopoietic system at all time points of investigation, as were macroscopic examinations for organ and tissue lesions. Animals which died during the study were examined for neoplastic changes. No treatment-related clinical signs of toxicity were observed. Body weight gain was retarded in the males of the top dose group from the very beginning of the study while in the males treated with 30 or 480 ppm the phenomenon occurred from study week 65 onwards. The females of the 120 ppm dose group exhibited an increase in body weight relative to controls starting at study week 35. At the 1920 ppm dose level, the males showed a temporary increase in food consumption from study weeks 28 to 50. Mortality was slightly higher in the males and females of the top dose group and the females of the lowest dose group than it was in the controls. As regards the haematological parameters, the males treated with 1920 ppm had reduced haematocrit values at the end of the study whereas the females receiving 480 ppm had reduced mean cell vo-

lume and haematocrit values from study month 6 but significantly increased mean cell haemoglobin concentration at study termination. In all dose groups and at all time points of investigation, the clinical chemistry results, organ weights and macroscopic findings were comparable with those observed in the controls. A non-neoplastic histopathological finding reported in males of the 480 and 1920 ppm dose groups consisted in interstitial cell infiltration in the kidney (no further details). Up to the highest test concentration of 1920 ppm in the feed (equivalent to approx. 290 and approx. 250 mg/kg body weight/day for males and females, respectively), no increase in the incidence of tumour-like changes was noted in males or females (Ogawa et al., 1989 a, b).

In range-finding carcinogenicity studies, (C57BL/6xC3H/ANF)F1 mice and (C57BL/6xAKR)F1 mice were treated by oral gavage with daily 100 mg/kg body weight doses of 2-mercaptobenzothiazole (as the commercial product Captax, purity not specified), formulated in 0.5-percent gelatine solution, at the age of 7 to 28 days and subsequently received 323 ppm 2-mercaptobenzothiazole mixed in feed (approx. 50 mg/kg body weight/day) for 17 months. Eighteen mice were studied per strain and sex. The dose corresponded to the maximum tolerated oral dose identified for dietary administration in a preliminary 19-day study. The animals which died during the administration phase and those sacrificed at the end of the study were examined macroscopically. Haematology was investigated only in animals with enlarged spleens or livers and/or lymphadenopathy. Histopathological examination of the liver, spleen, kidney, adrenal gland, stomach, intestine and genital organs was performed at the end of the study. The prematurely deceased animals were histopathologically examined on a case-to-case basis (no further details). The incidences of hepatomas, pulmonary tumours and lymphomas and the total number of tumour-bearing animals were statistically analysed in comparison with the pooled untreated and vehicle-treated controls. Tumour incidences were not significantly increased in either strain (Bionetics Research, 1968 a; Innes et al., 1969).

In a study conducted in parallel, groups of 18 male and 18 female (C57BL/6xC3H/ANF)F1 mice and (C57BL/6xAKR)F1 mice aged 28 days were given, into the nape of neck, a single subcutaneous injection of 2-mercaptobenzothiazole (as the commercial product Captax, in 0.5-percent gelatine solution) at 215 mg/kg body weight or (as the commercial product Rotax, formulated in dimethyl sulfoxide) at 1000 mg/kg body weight

and were subsequently placed under observation for 18 months. No details were given regarding the purity of the two commercial products investigated. Examination and statistical analysis of the findings were performed as in the oral study described above. Following administration of 215 mg/kg body weight, male (C57BL/6xC3H/ANF)F1 mice exhibited an increased incidence of lymphomas (reticulum cell sarcoma) which was not dose-related, while the total number of tumour-bearing animals and the incidences of hepatomas and pulmonary tumours were not higher than in the controls. Tumour incidences in female (C57BL/6xC3H/ANF)F1 mice treated with 215 mg/kg body weight as well as male and female (C57BL/6xAKR)F1 mice and mice receiving 1000 mg/kg body weight were in the range of the controls (Bionetics Research, 1968 a).

Cell transformation tests

The cell-transforming potential of 2-mercaptobenzothiazole was investigated in mouse fibroblasts (BALB/c-3T3 cells) according to a standard protocol for the cell transformation assay in three independent trials conducted in the absence of an exogenous metabolic activation system. The first assay, which was carried out with concentrations ranging from 0.074 to 0.294 mM, gave a limited negative test result. Cell transformation rate was not significantly increased at any of the concentrations tested; however, significant transformation was not even observed with the positive control chemical, benzo(a)pyrene, in this experiment. The second and third trials, which were carried out with comparable concentrations ranging from 0.066 to 0.265 mM and 0.0530 to 0.212 mM, respectively, both yielded equivocally positive results. The results were evaluated by the investigators as indicating limited activity, since in each case the cell transformation rate was significantly increased only at one concentration level (0.132 mM and 0.159 mM in the second and the third assay, respectively). In standard clonal survival assays and co-culture clonal survival assays performed in parallel, cell survival rates from trials 1 to 3 ranged from 49.0 to 0.0% and 84.5 to 0.275%, respectively, the survival rates for the concentration levels with significantly increased transformation rates being 7.55 to 19.3% and 23.8 to 19.9%, respectively. The LC_{50} for BALB/c-3T3 cells in the co-culture clonal survival assay was given as 0.13 mM. The overall test result was evaluated

as equivocal by the investigators, who recommended further tests (Matthews et al., 1993).

In an earlier cell transformation assay in BALB/3T3 cells, the 5 2-mercaptobenzothiazole (purity not specified) concentrations of 10.5, 21, 31.5, 42 and 63 µg/ml with respective cell survival rates of approx. 100, 70, 38, 20 and 0% induced neither significant nor concentration-dependent increases in the frequency of transformed cell foci. The negative and positive controls included in the study (culture medium and 3-methylcholanthrene, respectively) yielded the expected results (Litton Bionetics, 1982).

7.8 Reproductive toxicity

In the context of the U.S. Toxic Substances Control Act, the reproductive toxicity potential of 2-mercaptobenzothiazole was comprehensively investigated in accordance with the U.S. Environmental Protection Agency's testing guidelines in teratogenicity/embryotoxicity studies in the rat and the rabbit, in a two-generation study in the rat as well as in a dominant-lethal test in the rat. None of the studies produced any evidence of reproductive toxicity due to 2-mercaptobenzothiazole. Oral doses from 300 to 2200 mg/kg body weight and from 50 to 1500 mg/kg body weight were administered to rats and rabbits by gavage in the teratogenicity/embryotoxicity studies, and doses from 2500 to 15000 ppm were mixed into feed in the two-generation study and the dominant-lethal test in the rat. Dose ranges in each study also included maternally toxic doses, which in the rat resulted in reduced body weight gain and clinical signs of toxicity (≥ 600 mg/kg body weight and 2500 ppm in feed) and in the rabbit led to reduced body weight gain and increased liver weight, and at higher dose levels also increased mortality (≥ 150, lethal from 600 mg/kg body weight; Springborn Laboratories, 1989 a, b, c, d, 1990; Mercieca et al., 1991; Rodwell et al., 1990, 1991; see Table 10 in the appendix).

Even in earlier exploratory embryotoxicity/teratogenicity studies with intraperitoneal administration of the maximum tolerated dose to Sprague-Dawley rats and in an oral three-generation rat study with 5000 ppm 2-mercaptobenzothiazole mixed into feed the results were also negative as far as the chemical's reproductive toxicity was concerned (Hardin et al., 1981; FMC, 1957; see Table 10). In an embryotoxicity/teratogenicity study which

included monitoring of postnatal development in the ICR mouse following oral administration of 2-mercaptobenzothiazole at 1000 or 40 mg/kg body weight throughout gestation, the high dose group showed maternal toxicity (marked reduction in maternal body weight gain), an increase in the number of dead foetuses at an early stage (no precise details), reduced birth weights in the live pups and delayed ossification in the pups. Treatment had no effect on the incidences of external, skeletal or visceral anomalies or the pups' postnatal development up to 21 days after birth. The second dose group, treated with just 40 mg/kg body weight/day, showed no adverse treatment-related effects in either the dams or their offspring (Morita et al., 1979; see Table 10 in the appendix).

The relevance of an exploratory embryotoxicity/teratogenicity study which lacked consistent findings in different mouse strains was evaluated as equivocal even by the authors of the study. Following subcutaneous administration of a dose producing mild maternal toxicity (liver weight changes and retardation of body weight), findings in strain C3H were positive (intestinal displacement, wavy ribs, club foot, reduced foetal weight and reduced foetal crown-rump length), whilst in strain BL6 an initial study was also positive (alterations of the tongue, microphthalmia), but the findings were not reproducible in a second study performed in the same strain under identical experimental conditions, strain AKR giving negative results (Bionetics Research, 1968 b; see also Table 10 in the appendix).

A positive result from an embryotoxicity/dominant-lethal study, which is of doubtful validity because of poor experimental conduct and documentation (Aleksandrov, 1982), has been disproved by the clear negative results of a dominant-lethal test performed according to valid test guidelines as mentioned above (see Rodwell et al., 1991; Springborn Laboratories, 1989 e).

In an exploratory study on the reproductive toxicity of 2-mercaptobenzothiazole in embryonic chickens, doses in the range of 0.1 to 2.0 µmol/egg, formulated in acetone, were injected into the air chamber of eggs, onto the hearts of 3-day-old embryos (9 to 40 eggs/dose). A dose-independent increase in early embryo mortality (lethal 1 to 2 days after administration) was observed from 1.0 µmol/egg. At study termination on day 14 of incubation, dose-related malformations (of the eyes, wings, legs and neck, and open coelomic cavity) occurred in 11 to 30% of the surviving embryos at and above 0.1 µmol/egg (Korhonen et al., 1982, 1983). It is not possible to

extrapolate these findings to mammalian systems, however, because such comparison would fail to take into account the absorption barriers and detoxification mechanisms which exist in mammals. Furthermore, this test system is excessively sensitive and does not permit the distinction between teratogenic and embryolethal effects (Skofitsch, 1988; Neubert et al., 1992; Neubert, 1993; Heinrich-Hirsch, 1992).

7.9 Effects on the immune system

No information available.

7.10 Neurotoxicity

The neurotoxicity of 2-mercaptobenzothiazole was investigated in an acute study and a subchronic study in the Sprague-Dawley rat conducted in accordance with the U.S. Environmental Protection Agency's testing guidelines (EPA, 1985 a, 1987) as part of the U.S. Toxic Substances Control Act. No neurotoxicity was observed for 2-mercaptobenzothiazole in these studies. In the acute trial, single oral doses of 2-mercaptobenzothiazole, formulated in corn oil, were given by gavage at 0 (controls), 500, 1250 and 2750 mg/kg body weight, while in the subchronic study, doses of 0 (controls), 5000, 15000 and 25000 ppm (approx. 333, 1000 and 1667 mg/kg body weight/day, respectively) were administered in the feed for 13 weeks. Groups of 12 animals/dose level and sex underwent tests using a functional observational battery (FOB) and were examined for disturbances of motor activity (activity in the figure eight maze), and in the subchronic study, comprehensive neurohistological examinations were carried out. In the acute study, one female died after administration of the top dose, 2750 mg/kg body weight, and in both one male and one female, significant weight loss was noted relative to the control group one day after administration. Macroscopic examination at the end of the study, 14 days after administration, was without remarkable findings. During the FOB examinations, transient changes were noted up to 24 hours after administration (increased salivation after one hour in the top dose males and in the females of all dose groups, reduced vocalisation in the top and the mid dose males after 1 to 6 hours and urinary staining in the top dose females 24 hours after dosing). All other FOB results, particularly those for the quantitatively

assessable parameters, grip strength and hindlimb splay after a drop from 30 cm, were comparable with controls at all time points of examination (up to 14 days after dosing). Motor activity was reduced in both sexes in the top dose group and in the mid dose females 12 hours after dosing. Discussing their findings, the investigators considered the study results to be attributable to generalised toxicity rather than specific neurotoxicity. In the subchronic study, the two top dose groups, receiving 15000 and 25000 ppm 2-mercaptobenzothiazole in the feed, showed treatment-related depression of body weight gain in association with reduced food intake. Neither the FOB assessments for CNS disorders, altered muscle tone, equilibrium and sensory function, the motor activity tests nor histopathological examination of nerve tissue showed any evidence of a neurotoxic potential of 2-mercaptobenzothiazole (Bio-Research, 1989 a, b, 1990; Bannister et al., 1991).

The clinical signs of toxicity seen upon acute oral or intraperitoneal administration to mice (marked peripheral vasodilation, extensive salivation, lacrimation and tonic-clonic convulsions) led the investigators of an older study to conclude that 2-mercaptobenzothiazole had an effect on the central nervous system. Another finding which, according to the investigators' discussion, suggested activity in the central nervous system was that pretreatment with phenobarbital totally blocked the convulsions and salivation while reducing the severity of the peripheral vasodilation. As pretreatment with atropine sulphate failed to block the salivation and caused only a slight reduction of the peripheral vasodilation, the investigators discussed the possible cholinergic activity of 2-mercaptobenzothiazole (see also Table 2 in the appendix; Guess and O'Leary, 1969).

In-vitro and in-vivo studies were carried out to investigate the effect of 2-mercaptobenzothiazole on the catecholamines and the chemical's inhibitory action on dopamine β-hydroxylase activity. Male CF1 mice had altered brain catecholamine levels at 1 and 2 hours following intraperitoneal administration of 2-mercaptobenzothiazole at 300 mg/kg body weight (a drop in noradrenaline levels to approx. 60% and rises in dopamine levels to 110 and 123%, respectively, were seen relative to controls). Shortly after administration, the animals exhibited extreme depression, accompanied by ptosis extended after 2 hours. Both the clinical picture and the noradrenaline and dopamine concentrations in brain were comparable with controls again after 4 hours. In a parallel study, male mice also received 2-mercaptobenzothiazole at 300 mg/kg body weight by intraperitoneal injection and, star-

ting 10 minutes after dosing, had their motor activity assessed at 30-minute intervals for a total period of 4 hours. The methylcellulose-treated vehicle controls initially displayed very marked motor activity but this fell rapidly in the first hour after dosing, the mice remaining relatively inactive for the remainder of the experiment. In the animals treated with 2-mercaptobenzothiazole the initially high activity was absent. After about 2 hours, however, spontaneous activity in these animals increased, the increase coinciding with the normalisation of noradrenaline levels described above. Male Sprague-Dawley rats (weighing 180 to 190 g) were treated with metaraminol (5 mg/kg given intraperitoneally as the bitartrate) in order to deplete heart noradrenaline stores by approx. 80%. After 18 hours, the animals were injected intraperitoneally with 300 mg 2-mercaptobenzothiazole/kg body weight, and after another 30 minutes they were given 35 mg dopamine/kg body weight. Controls were treated with either the plain vehicle, metaraminol or metaraminol and dopamine. After 3 hours, the myocardial noradrenaline concentration measured in the animals treated with metaraminol and dopamine recovered to 60% of the vehicle control level, whilst the noradrenaline levels found in animals treated with metaraminol alone, metaraminol and 2-mercaptobenzothiazole or metaraminol, 2-mercaptobenzothiazole and dopamine showed no significant differences and were only approx. 17 to 20% of the vehicle control. Administration of 2-mercaptobenzothiazole thus blocked conversion of dopamine to noradrenaline. In vitro, the activity of dopamine β-hydroxylase isolated from bovine adrenal medulla was non-competitively inhibited by 2-mercaptobenzothiazole concentrations of 10^{-5} and 5×10^{-6} mol/l by 72 and 47%, respectively. The mechanism discussed by the investigators to explain the effect of 2-mercaptobenzothiazole on catecholamine metabolism involves chelation of copper by 2-mercaptobenzothiazole, thus reducing the activity of the copper-containing enzyme dopamine β-hydroxylase, and hence inhibiting oxidation of dopamine to noradrenaline (Johnson et al., 1970).

7.11 Other effects

Under the name Mebethisol, pharmaceuticals containing 2-mercaptobenzothiazole as their active ingredient were developed in the former Soviet Union for treatment of mycotic infections and hepatobiliary system disorders. According to the investigators, Mebethisol reportedly possesses

broad antimycotic and antibacterial activity, causes practically no adverse effects and even acts as a hepatoprotectant (Gladyshev et al., 1991; Golovkin et al., 1989; Koryakovskij et al., 1992; Litvinchuk et al., 1977). In the dog and the Wistar rat, single and chronic intravaginal administration of Mebethisol in the form of vaginal tablets (single dose of 2400 mg/kg body weight or treatment with 50, 400 or 1000 mg/kg body weight for 1, 2 or 3 months, content of active substance probably 20%, no clear details) did not result in any changes in general condition, electrocardiogram, haematological parameters, hepatic function, renal function, morphology or histology (Gladyshev et al., 1991). In cats and guinea pigs which were experimentally infected with *Microsporum canis*, treatment with 5-percent solutions of Mebethisol (two daily oral doses of 3 and 1 ml, respectively) reportedly completely cured the infection within 12 days without adverse effects of treatment (clinical picture, blood count, liver function tests, ECG; Koryakovskij et al., 1992). No binding of Mebethisol to serum proteins isolated from human blood was found by equilibrium analysis in vitro (Gladyshev et al., 1988). On the whole, the Mebethisol studies discussed above are mostly very poorly documented and not suitable for evaluation of the toxicological and pharmacological potential of 2-mercaptobenzothiazole.

When 2-mercaptobenzothiazole was administered as a single dose of 2500 mg/kg body weight (as the commercial product Kaptax, purity not specified, probably given intraperitoneally), SVA mice reportedly showed altered activity of antigen-specific T suppressors (no further details), increased proliferation potential of haematopoietic stem cells and a shift in their differentiation towards erythropoiesis (Istamov et al., 1990 a, b).

In-vitro cytotoxicity tests were carried out by applying 2-mercaptobenzothiazole (purified commercial product Rotax) as a dry powder, a suspension in cottonseed oil (1.5 to 12 mg/ml) or a saturated aqueous saline solution (0.5 mg/ml) to monolayers of the mouse fibroblast cell line L-929 and cultures of 10-day chicken embryo cells. The cells were stained with a vital dye, the release of which was considered a sign of cytolethality. 2-Mercaptobenzothiazole, as a powder, had a lethal effect on L-929 cells, while the oil suspension was lethal to L-929 and chicken embryo cells at concentration levels ≥ 3 and ≥ 6 mg/ml, respectively. No lethal effect was observed with the saturated aqueous saline solution. In a further study on L-929 cells, 6-hour incubation with 2-mercaptobenzothiazole (at 0.25 mg/ml culture

medium) was observed to cause marked vacuolisation, and at 14 hours cell lysis was noted (Guess and O'Leary, 1969).

For V79 cells of the Chinese hamster, the IC_{50} (concentration which is toxic to 50% of the cells when incubated for 7 days) was determined as 49 µg/ml (Nakamura et al., 1990).

At a concentration of 1 mM (3-day incubation period), 2-mercaptobenzothiazole was highly cytotoxic to Ehrlich ascites tumour cells, whereas at 10 µM it did not affect cell survival rate (Takamura et al., 1989).

8 Experience in humans

Peak 2-mercaptobenzothiazole levels were found in the urine of patients 8 hours after administration of Mebethisol (a drug containing 2-mercaptobenzothiazole, see Section 7.11), as was the case in parallel studies carried out in rats and rabbits which received single oral Mebethisol doses of 250 mg/kg body weight by gavage (no further details; Litvinchuk et al., 1977).

Skin irritation

2-Mercaptobenzothiazole is not irritating to the human skin. A 50-percent formulation of the commercial product Thiotax (purity not specified, in dimethyl phthalate), was applied occlusively to the skin of 50 human volunteers 3 times/week in a series of fifteen 24-hour exposures. None of the subjects developed skin irritation from this treatment (Product Investigations, 1976).

Skin sensitisation

2-Mercaptobenzothiazole has a skin-sensitising effect in humans and has been assigned to category A, important contact allergens, by the Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (BgVV; Federal Institute for Consumers' Health Protection and Veterinary Medicine) in the Federal Republic of Germany (Kayser and Schlede, 1995; Klaschka and Voßmann, 1995). The contact-allergic skin reaction to 2-mercaptobenzothiazole is characterised by eczematous contact dermatitis which is limited to the contact area, occurs with delay after exposure and, as far as is known from studies, is not associated with elevated IgE levels

(type-IV allergy). Skin lesions of this type have been reported after contact with rubber and latex products that contained 2-mercaptobenzothiazole, such as gloves, shoes, finger cots, clothing and medical prostheses. As 2-mercaptobenzothiazole is listed in what is known as the rubber allergen series and in international standard series of patch tests (e. g. the International Contact Dermatitis Research Group (ICDRG) standard series), numerous case reports and results from large cohorts exist on patch test reactions to 2-mercaptobenzothiazole (see Table 11 in the appendix). In patch test series conducted in workers at rubber processing plants, 11 out of 1088 individuals (1%) had positive reactions to 2-mercaptobenzothiazole (Ziegler and Süß, 1974/75). In routine tests carried out at dermatology centres irrespective of whether or not contact allergy to rubber products was suspected, approx. 0.3 to 2.9% of patients had a positive reaction to 2-mercaptobenzothiazole. Of the patients found to have positive patch test reactions to rubber products and/or rubber chemicals, approx. 1.8 to 30% showed positive reactions to 2-mercaptobenzothiazole (see Table 11). In addition, patients who had positive reactions to 2-mercaptobenzothiazole in the standard patch test mostly also reacted to other so-called rubber chemicals, such as thiurams, carbamates, phenylenediamines (Edman, 1991; Foussereau and Cavelier, 1977; von Hintzenstern et al., 1991), and as regards latex products, they also reacted to natural latex from the rubber tree (*Hevea brasiliensis*; Groß, 1990; Guimaraens et al., 1992). The majority of patients also showed positive reactions to mercapto mix and derivatives of 2-mercaptobenzothiazole, where tested (see e. g. Foussereau et al., 1983; Fregert, 1969; Lynde et al., 1982 a, b, c; Mitchell et al., 1976). Reactions of the immediate type, characterised by anaphylactic reactions such as skin lesions occurring directly on contact, allergic rhinitis, signs and symptoms of asthma, circulatory alterations to the point of allergic shock and, where studied, IgE elevations (type-I allergy) such as have been reported after contact with latex products containing 2-mercaptobenzothiazole (surgical gloves, condoms, etc.), are attributable to natural-rubber latex rather than 2-mercaptobenzothiazole (see e. g. Axelsson et al., 1987; Carrillo et al., 1986; Ehl et al., 1988; Frosch et al., 1986; Groß, 1990; Guimaraens et al., 1992; Kleinhans, 1984 a; Seifert et al., 1987). In order to be certain to elicit positive patch test reactions in individuals with known sensitivity to 2-mercaptobenzothiazole, it was necessary to apply the chemical at concentrations of 0.316% in petrolatum, equivalent to 145 µg/cm² skin. In some patients, positive reactions were obtained even with 0.1% (45 µg/cm² skin;

Emmett et al., 1994). In dermatologically healthy subjects, 2-mercaptobenzothiazole caused moderate sensitisation in the maximisation test, while there was no sensitisation in the patch test with repeated application (Kligman, 1966; Magnusson and Kligman, 1970; Monsanto, 1987; Product Investigations, 1976; see also Table 11). A recommendable review article on the skin-sensitising potential of 2-mercaptobenzothiazole in humans was published by Feinman (1987).

Epidemiological carcinogenicity studies

A total of 1059 workers at a rubber chemicals plant in Nitro, West Virginia (USA), were examined in an epidemiological study to find whether they had increased mortality from cancer associated with exposure to 2-mercaptobenzothiazole and/or derivatives of 2-mercaptobenzothiazole (sodium 2-mercaptobenzothiazole, N-cyclohexyl-2-benzothiazole sulphenamide, benzothiazyl disulphide, N-tertiary-butyl-2-benzothiazole sulphenamide, 2-(morpholinothio) benzothiazole, 2-(2,6-dimethylmorpholinothio) benzothiazole, 2-(hexamethyleneiminothio) benzothiazole and 1,3-bis-(2-benzothiazolylmercaptomethyl) urea). There were indications of a possible connection between malignant tumours of the urinary bladder and the exposure to 2-mercaptobenzothiazole and/or its derivatives. However, in addition to 2-mercaptobenzothiazole and its derivatives, the production of which started at the plant in 1934 and still continued at the time of the study, p-aminobiphenyl was also used between 1935 and 1955. p-Aminobiphenyl is a compound which the investigators discussed as reportedly being a possible potent bladder carcinogen after short-term exposure. The study cohort included white male production workers who were hired at some point after the plant had been established and who were active at the plant between 1955 and 1977 for one day or more. Exposure to derivatives of 2-mercaptobenzothiazole was assumed to be equivalent to 2-mercaptobenzothiazole exposure. A total of 600 workers had exposure to 2-mercaptobenzothiazole and/or its derivatives. For these individuals, cumulative exposure indices were calculated on the basis of documented work histories, workplace sampling data from 1977 and 1989 and the respective durations of occupation. Exposure to 2-mercaptobenzothiazole and/or its derivatives was highest during the period between 1943 and 1954, being > 2 < 3 mg/m³ on average. As shown in a graphical representation, it was ≤ 1

mg/m³ in other years and dropped to less than 0.25 mg/m³ after 1970 (see Collins et al., 1999, below). Because of concern about the potential confounding effect of exposure to p-aminobiphenyl with regard to tumour findings, workers with p-aminobiphenyl exposure were identified separately. Those employees whose work covered all parts of the plant, such as yard labour, maintenance, or general production jobs, were not considered exposed to p-aminobiphenyl. As discussed by the investigators in a later section, however, the possibility could not be precluded with certainty that there was some, if only short-term, exposure to p-aminobiphenyl in these cases. Standardised mortality ratios (SMRs) were calculated for the period from 1 January 1955 to 31 December 1987. The white male populations of the counties located within a 20-mile radius of the plant and the United States as a whole served as reference cohorts. Compared with the local reference cohort, mortality from all causes was reduced in the 600 workers with 2-mercaptobenzothiazole exposure, but mortality from all cancers and mortality from lung, prostate and bladder cancers was raised. The subcohort of workers exposed to 2-mercaptobenzothiazole and p-aminobiphenyl (89 workers) also showed increased mortality from all cancers and increased mortality from lung cancer (10 deaths observed, 3.4 expected cases) and particularly from bladder cancer (7 deaths observed, 0.22 expected), while there were no deaths from prostate cancer in this subgroup. The subcohort of workers exposed to 2-mercaptobenzothiazole but not to p-aminobiphenyl (511 workers) showed reduced mortality from all cancers and lung cancer but again mortality from bladder cancer (3 deaths observed, 0.66 expected) was increased, as was mortality from prostate cancer (4 deaths observed, 1.99 expected). Workers who were hired only after 1955, when p-aminobiphenyl production was stopped (270 of the 600 workers exposed to 2-mercaptobenzothiazole), had a lower mortality from all cancers than the local reference cohort, none of the 8 deaths occurring in total in this group being attributable to bladder cancer or other cancers (0.03 and 4.26 expected deaths, respectively). In regard of cumulative exposure to 2-mercaptobenzothiazole, there were no associations between the prostate cancer incidences and exposure categories, and unexposed workers were found to have comparable prostate cancer incidences. Therefore the investigators suggested that these tumours were caused by an unknown extraneous factor, which was affecting all workers equally and thus was independent of 2-mercaptobenzothiazole. The investigators critically reviewed 3 deaths from bladder cancer in the cohort exposed to 2-mercaptobenzothia-

zole but not to p-aminobiphenyl. As indicated by the cumulative exposure indices, the 3 workers had been in the two highest categories of cumulative exposure to 2-mercaptobenzothiazole. There was no strong trend to indicate dose-dependency of the disease. However, the investigators discussed the fact that in principle it was not possible to establish a meaningful, statistically significant dose-dependent trend based on only 3 cases. The 3 cases of cancer all occurred at least 20 years after the first exposure, and all 3 workers were employed at the plant even before 1956, that is at a time when p-aminobiphenyl was still being used. Although the 3 workers were categorised as not having had exposure to p-aminobiphenyl, ultimately, due to their respective jobs in yard labour, general production work and maintenance, the possibility cannot be precluded with certainty that they may have had at least short-term exposure to p-aminobiphenyl. The investigators recommended further follow-up of the cohort (Strauss et al., 1993).

As recommended, the cohort from Nitro, West Virginia (USA; Strauss et al., 1993, see above), was followed up. From the results of the study update, which added 9 years of additional follow-up to the original observation period, it seems that 2-mercaptobenzothiazole did not increase the rates of cancers, including cancer of the prostate and lung. The study does not allow any definite conclusion with regard to the potential of 2-mercaptobenzothiazole to cause bladder cancer because of the possibility that there was additional exposure to the potent bladder carcinogen p-aminobiphenyl, and due to statistical considerations. The standardised mortality ratios (SMRs) calculated for the 600 workers with exposure to 2-mercaptobenzothiazole and/or derivatives of the chemical during the period from 1 January 1955 until 31 December 1996, in contrast to the earlier examination of the cohort, no longer indicated any increased mortality from all cancers or from lung or prostate cancer (mortality from all cancers: SMR 1.0 (95% confidence interval 0.8 to 1.3), 63 deaths observed, 63.9 expected (earlier study: 46 deaths observed, 38.81 expected); from lung cancer: SMR 1.0 (95% confidence interval 0.7 to 1.5), 27 deaths observed, 26.1 expected (earlier study: 21 deaths observed, 15.92 expected); from prostate cancer: SMR 0.9 (95% confidence interval 0.2 to 2.3), 4 deaths observed, 4.4 expected (earlier study: 4 deaths observed, 1.9 expected)). As in the earlier study, mortality from urinary bladder cancer was markedly increased (SMR 8.9 (95% confidence 4.7 to 15.2), 13 deaths observed, 1.5 expected (earlier study: 10 deaths observed, 0.88 expected)). This increase in mortality from

bladder cancer was noted both in the subcohort of 89 workers with exposure to p-aminobiphenyl (SMR 27.1 (95% confidence interval 11.7 to 53.4), 8 deaths observed, 0.3 expected (earlier study: 7 deaths observed, 0.22 expected)) as well as the in the subcohort of 511 workers classed as not having been exposed to p-aminobiphenyl (SMR 4.3 (95% confidence interval 1.4 to 10.0), 5 deaths observed, 1.2 expected (earlier study: 3 deaths observed, 0.66 expected)). However, the fact that the subcohort of 511 workers was classed as not exposed to p-aminobiphenyl was critically reviewed by the investigators of the follow-up study, as a number of the workers must be considered to have had potential exposure to p-aminobiphenyl (yard labourer, plantwide production worker, maintenance worker). As elaborated by the authors in the discussion section, the unknown degree of exposure to the known bladder carcinogen p-aminobiphenyl, makes it impossible to estimate the risk of bladder cancer due to 2-mercaptobenzothiazole exposure in this subcohort. All 5 workers from this subcohort who died of bladder cancer had held plantwide jobs for 1, 5, 8 or 20 months and 10 years, and thus it cannot be precluded that their responsibilities may have involved exposure to p-aminobiphenyl. Among the 270 workers with exposure to 2-mercaptobenzothiazole and/or its derivatives but definitely without exposure to p-aminobiphenyl as they were not hired until after 1955 – after p-aminobiphenyl use at the plant was discontinued – there were no deaths from bladder cancer (SMR 0.0 (95% confidence interval 0.0 to 24.70), 0 deaths observed, 0.2 expected). The absence of urinary bladder tumours in this subcohort suggests that 2-mercaptobenzothiazole lacks urinary bladder carcinogenicity; nevertheless, based on statistical considerations (only 0.2 expected deaths), it cannot be stated with certainty that 2-mercaptobenzothiazole is not a bladder carcinogen (Collins et al., 1999).

In an epidemiological study conducted in parallel in a total of 2410 workers at a plant producing rubber chemicals (vulcanisation inhibitors and accelerators, antioxidants and other chemicals) in Wales, there was no indication of increased tumour-induced mortality due to exposure to 2-mercaptobenzothiazole. The plant first produced 2-mercaptobenzothiazole in 1932, operations also involving sodium 2-mercaptobenzothiazole and zinc 2-mercaptobenzothiazole, while production of the 2-mercaptobenzothiazole derivatives, dibenzothiazyl disulphide, N-oxydiethylene-2-benzothiazolsulphenamide and N-cyclohexyl-2-benzothiazolsulphenamide began in 1939. Apart from exposures to 2-mercaptobenzothiazole and/or 2-mercaptobenzothia-

zole derivatives (360 workers), exposure to polymerised 2,2,4-trimethyl-1,2-dihydroquinoline (213 workers), N-cyclohexylthiophthalamide, phenyl-β-naphthylamine (94 workers) and aniline or o-toluidine (409 workers) was examined more closely. Standardised mortality ratios (SMRs) were calculated for the period from 1 January 1955 to 31 December 1986. All workers were included who had at least 6 months' exposure and were already in employment on 1 January 1955 (1549 men, 86 women) or were hired by 31 December 1984 (611 men, 164 women). On the basis of individual job histories and classifications of the various job and department titles as zero exposure, very low (0 to 1 mg/m³), low (1 to 2.5 mg/m³), medium (2.5 to 6 mg/m³) and high (6 to 20 mg/m³) exposure, each worker's individual total exposure to 2-mercaptobenzothiazole and/or its derivatives was determined. Monitoring measurements were carried out from 1977 onwards. The population of England and Wales as a whole and the population of Denbighshire, the county in which the plant was situated, served as reference cohorts. The overall mortality from all causes and the overall mortality from neoplasms were calculated under the aspect of the beginning of exposure and corresponded to, or were lower than, the expected mortalities (referred to as the healthy worker effect). Analysis of the mortality data by site of cancer revealed no statistically significant differences from the reference cohorts. In addition, there was no statistically significant increase in mortality from bladder cancer, a finding which is in contrast to the epidemiological study discussed above which was conducted in parallel at an American plant (Strauss et al., 1993). Of the total of 360 workers with exposure to 2-mercaptobenzothiazole and/or its derivatives, 119 died in the period on which the calculations were based, 3 of whom died of bladder cancer (1.1 expected deaths), of whom 2, in turn, also had exposure to aniline and/or o-toluidine. In the discussion of their findings, the investigators addressed the fact, however, that analysis by site of cancer provided little information for confident interpretation due to the small numbers of site-specific deaths (Monsanto, 1992; Sorahan and Pope, 1993). Note: The two available documents on this study contain slight differences in data. Almost all of the data presented above were taken from the publication by Sorahan and Pope (1993).

The cohort of 2160 male workers investigated in the study by Monsanto (1992) and Sorahan and Pope (1992) was re-examined 10 years later. In the follow-up study, the mortality and cancer morbidity among the workers

was calculated for the 1955–1996 and 1971–1992 periods, respectively, in relation to the total study cohort but also in relation to the subcohorts with exposure to 2-mercaptobenzothiazole and its derivatives (357 workers), aniline (385 workers), phenyl-β-naphthylamine (94 workers) and/or o-toluidine (53 workers).

The subcohort encompassing all 4 chemicals consisted of only 605 workers, from which it follows that numerous workers had exposure to more than one of the above-mentioned chemicals and were allocated to several single-chemical subcohorts. For 2-mercaptobenzothiazole, it was possible to estimate individual cumulative overall exposure (Monsanto, 1992; Sorahan and Pope, 1992, see above), whilst for the other chemicals it was only possible to ascertain individual total duration of employment in the respective production departments without obtaining an estimate of exposure level. As in the first study, the cancer site-specific mortalities found for the total study cohort of 2160 workers were in the range of expected values, or lower. In contrast to the first study, however, there was no significant increase in the number of deaths from bladder cancer (SMR 141, 17 deaths observed, 12.1 expected). In the subcohort of workers with exposure to 2-mercaptobenzothiazole, phenyl-β-naphthylamine, o-toluidine and/or aniline, bladder cancer mortality and malignant bladder cancer morbidity were significantly increased (SMR 277 (95% confidence interval 127 to 526), 9 deaths observed, 3.25 expected; SMR for malignant bladder diseases 208 (95% confidence interval 104 to 371), 11 deaths observed, 5.3 expected). In the single-chemical subcohorts, mortality from bladder cancer was significantly increased in the subcohorts with exposure to 2-mercaptobenzothiazole (SMR 408, 7 deaths observed, 1.72 expected), phenyl-β-naphthylamine (SMR 641, 4 deaths observed, 0.62 expected) and o-toluidine (SMR 1589, 3 deaths observed, 0.19 expected) while it was nonsignificantly increased in the subcohort with aniline exposure (SMR 200, 4 deaths observed, 2.00 expected), though there was multiple allocation of some deaths. The majority of workers who died of bladder tumours had already had exposure before 1955 and died > 20 years after first exposure. The increased mortality from cancer of the large intestine (7 deaths observed, 2.73 expected) in the subcohort exposed to 2-mercaptobenzothiazole was suggested by the investigators to be a chance finding or a consequence of nonoccupational factors. In order to identify more precisely the noxious agent actually causing bladder cancer, the investigators calculated the relative risk

of bladder cancer in relation to cumulative overall exposure (for 2-mercaptobenzothiazole) and duration of employment in the various production departments (for the other 3 chemicals). The relative risk of dying of bladder cancer or developing malignant and/or benign bladder neoplasms showed a significant positive trend and rose with the duration of employment in the phenyl-β-naphthylamine and o-toluidine production departments. In the case of 2-mercaptobenzothiazole and aniline, relative risk was not found to be dependent upon cumulative overall exposure or duration of employment. The investigators interpreted the study results as indications that the increased incidence of bladder cancer in the workers employed in the 2-mercaptobenzothiazole, aniline, o-toluidine and/or phenyl-β-naphthylamine production departments is probably related to occupation, though the agent actually causing bladder cancer could not be identified with certainty. They suspected that phenyl-β-naphthylamine was the most likely actual cause of increased bladder cancer, or that cancer was caused by a component used in the course of phenyl-β-naphthylamine production, which also involves the known bladder carcinogen β-naphthylamine, or possibly also by a component used in o-toluidine production. The presence of a bladder carcinogen in the 2-mercaptobenzothiazole production process was considered unlikely by the investigators as the relative risk of developing bladder cancer did not depend on cumulative overall exposure to the chemical (Sorahan et al., 2000).

9 Classifications and threshold limit values

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) has assigned 2-mercaptobenzothiazole to category 3 of carcinogenic working substances, i.e. the category of “substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data”, and to pregnancy risk group C, i.e. substances for which “there is no reason to fear a risk of damage to the embryo or foetus when MAK and BAT values are observed”. The Commission has set the MAK value (maximum workplace concentration) at 4 mg/m³ I (i. e. measured as the inhalable fraction of the aerosol) and designated the substance with “Sh” on account of its sensitising potential (DFG, 2000; Greim, 2000).

The toxicology advisory council (“Beraterkreis Toxikologie”) to the hazardous substances committee (“Ausschuss für Gefahrstoffe” (AGS)) has not assigned 2-mercaptobenzothiazole to any of the three carcinogenicity categories. Following adoption by the AGS of the toxicology advisory council’s proposal for classification (expected in 2001), 2-mercaptobenzothiazole would not be legally classified in the Federal Republic of Germany.

Appendix

Beginning of Table 1

Table 1. Comparative studies on the toxicokinetics and metabolism of 2-mercaptobenzothiazole in accordance with the EPA Test Rule (EPA, 1985 b; El Dareer et al., 1989; SoRI, 1986 a, b, c, 1987 a, b)

a) Single and repeated oral administration and single intravenous administration in the Fischer-344 rat

	0.592 mg/kg b.w. single oral dose		55.5 mg/kg b.w. single oral dose		approx. 0.5 mg/kg b.w. repeated oral dose (15 days)		0.602 mg/kg b.w. single i.v. dose	
	males	females	males	females	males	females	males	females
Excreted in urine within 8 hours	53–63	16–64	43–85	20–69	15–52	49–59	47–95	69–101
8–24 hours	13–25	1–14	18–35	15–32	15–59	31–48	7–30	4–16
24–48 hours	0.2–4.9	1.7–4.8	1.8–6.4	3.2–5.9	4.1–8.2	3.8–5.1	0.7–6.5	0.7–2.7
48–72 hours	0.2–1.3	0.3–4.0	0.3 –1.9	0.7–2.0	2.6–5.8	1.1–1.6	0.4–1.5	0.6–1.4
72–96 hours	0.05–0.17	0.15–0.29	0.17–0.54	0.78–1.70	1.08–3.21	0.55–0.87	n.a.	n.a.
Total excretion at 96 hours in urine	93 ± 6.9	72.1 ± 17.8	106 ± 14	103 ± 23	90.7 ± 8.9	101 ± 4	90.9 ± 9.2	96.1 ± 8.1
in faeces	9.2 ± 2.36	5.9 ± 2.4	5.56 ± 0.88	4.03 ± 1.59	9.99 ± 1.75	5.22 ± 0.46	15.1 ± 11.4	3.79 ± 2.17
(% of administered radioactivity, rounded values in some cases, total value for urine plus cage rinses)							(within 72 hours)	
Half-lives (hours) for the α and β phases of elimination								
from whole blood α	4.53	6.45	2.96	2.16	4.7	8.56	0.8	0.74
β	439	559	76600	105	6000	5780[1)]	2320	129
from plasma α	4.01	4.01	3.03	3.2	4.13[1)]	3.73	1.06	1.06
β	87.4	66	72.9	95	312	79.6	22.1	54.9
Tissue activity after 8 hours in the body[2)]	n.a.	n.a.	n.a.	n.a.	8.181	4.486	n.a.	n.a.
whole blood	2.27	2.37	1.39	1.25	3.29	1.93	9.19	8.03
plasma	1.08	0.939	0.799	0.636	2.05	0.924	8.39	5.46
(% of radioactivity administered)							(after 1 hour)	
Residual activity at study termination, in the body[3)]	n.a.	n.a.	n.a.	n.a.	1.918	1.546	n.a.	n.a.
whole blood	1.29	1.35	0.42	0.51	1.53	1.2	1.74	1.52
plasma	0.033	0.055	0.009	0.012	0.036	0.028	0.045	0.055
(% of radioactivity administered)	(after 96 hours)		(after 96 hours)		(after 96 hours)		(after 72 hours)	
Total recovery	103 ± 7	79.3 ± 18.8	112 ± 14	108 ± 24	n.a.	n.a.	108 ± 10	102 ± 7
(% of radioactivity administered)								
Metabolites	a total of 7 possible metabolites, 2 of which were major metabolites, traces of MBT and MBTS (identified only in one animal/sex)				2 metabolites (one thioglucuronide and a metabolite which was presumably oxidised at the SH group, no MBT or MBTS)		a total of 4 metabolites, 2 of which were major metabolites, traces of MBT (identified only in one animal/sex)	

Table 1. Comparative studies on the toxicokinetics and metabolism of 2-mercaptobenzothiazole in accordance with the EPA Test Rule (EPA, 1985 b; El Dareer et al., 1989; SoRI, 1986 a, b, c, 1987 a, b)

b) Single dermal application in the Fischer-344 rat and the Hartley guinea pig

	24.7 µg/animal, 48 hours[4)]		24.7 µg/animal, 48 hours[4)]	36.1 µg/animal, 96 hours		36.1 µg/animal, 96 hours
	occlusive, rat		occlusive, guinea pig	occlusive, rat		occlusive, guinea pig
	2 males	2 females	2 females	males	females	females
Absorption	24.57	14.16	20.35	16.1	17.5	33.4
(% of radioactivity administered)	(combined urinary and faecal excretion)			± 2.8	± 1.9	± 8.2
				(combined urinary and faecal excretion and content in whole blood (blood mass 9% of body mass))		
Total excretion in urine	22.2–24.1	13.1–14.5	16.6–23.5	14.7	16.5	32.6
in faeces	1.26–1.57	0.112–0.608	0.037–0.558	0.98	0.64	0.369
(% of administered radioactivity, total value for urine plus cage rinses)	(each within 48 hours)		(within 48 hours)	(each within 96 hours)		(within 96 hours)
Residual activity after 96 hours, in the body	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
whole blood	n.a.	n.a.	n.a.	0.367	0.362	0.332
plasma	n.a.	n.a.	n.a.	0.029	0.028	0.040
bound at the site of application[4)]	n.a.	n.a.	n.a.	61.5	51.6	15.8
removable from the application site by washing[4)]	n.a.	n.a.	n.a.	9.12	12.8	47.3
detectable at the application site	69.6–76.2	81.4–88.7	62.9 (1 animal)	–	–	–
(% of radioactivity administered)	(unwashed skin plus covering material)					
Total recovery	95–99.9	96.5–102	79.5 (1 animal)	86.6	81.9	94.4[1)]
(% of radioactivity administered)				± 6.0	± 10.3	± 5.2

1) There are minor differences between the various publications; the data given above were taken from the respective original study reports (SoRI, 1986 b, 1987 a, b).

2) including blood concentrations; at the first time point of assessment (8 hours), the concentrations (nCi/ml or g, as the case may be) found in the examined organs and tissues were in the following order: males: kidney > thyroid gland > liver > plasma > blood > lung > bone marrow > heart > spleen > fat > gonads > muscle > brain > bone; females: thyroid gland > kidney > blood > plasma > liver > bone marrow > lung > gonads > heart > spleen > fat > muscle > brain > bone.

3) including blood concentrations; the highest organ and tissue concentrations were the respective levels of 6.49 and 7.26 nCi/g found in the thyroid gland, representing 0.001% of the administered radioactivity.

4) preliminary studies with cleansing of the application site (rat 2 cm², guinea pig 5 cm²) at the end of the exposure period (48 hours); it was demonstrated in 2 other animals/sex that thorough cleansing (soapy water (1% detergent), ethanol, brush) 10 minutes after application was still able to remove approx. 70% (rat) or approx. 77% (guinea pig) of the applied radioactivity.

n.a. not assayed
MBT 2-mercaptobenzothiazole
MBTS 2-mercaptobenzothiazole disulphide
b.w. body weight

End of Table 1

Beginning of Table 2

Table 2. Acute toxicity of 2-mercaptobenzothiazole

Species, strain, sex[a)]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat, Sprague-Dawley, male, female	oral	23000*	no data	LD_{50}; drowsiness and collapse; necropsy of deceased animals: lung congestion, swollen intestinal walls and pale liver with discoloured areas	no data	Scientific Associates, 1956
* The dose was administered as a 25% aqueous solution, given in 2 or 3 portions within one day. The investigators state that administration of an emulsion was observed to increase toxicity (LD_{50} 8000 to 10000 mg/kg body weight (no precise details)).						
Rat, albino	oral	11804	no data*	LD_{50}	no data	Datsenko and Korneychuk, 1993
* Test substance was the commercial product Captax.						
Rat, Wistar, male	oral	7300–9400*	no data*	LD_{50}; humpback behaviour, rough coats; terminal necropsy was without findings	14 days	CIVO TNO, 1977
* Test substances were 5 different batches of 2-mercaptobenzothiazole, formulated in propylene glycol (no further details), the resulting LD_{50} values being 7300, 8400, 8600, 9300 and 9400 mg/kg body weight.						
Rat, albino	oral	6000–7000	no data	lethal within 2 days	7 days	Litvinchuk, 1963
Rat, Sprague-Dawley, male, female	oral	ca. 5000	no data*	LD_{50}; ataxia, piloerection, reduced activity, breathing difficulties (irregular breathing, dyspnoea); necropsy of the animals which died and those which survived to the end of the study was without findings	14 days	Sumitomo, 1977
* Test substance was the commercial product Soxinol M, formulated in corn oil.						
Rat, male	oral	> 3980	no data*	LD_{50}; mortality 0/2 at 3980 mg/kg body weight; terminal necropsy findings included kidney changes from 252 mg/kg body weight and liver changes from 500 mg/kg body weight (no precise details)	14 days	Dow, 1961
* Test substance was the commercial product Captax, formulated in corn oil.						
Rat, Sprague-Dawley, male, female	oral	3800	97.4%*	LD_{50}; reduced food consumption and hypoactivity, weakness, collapse; necropsy of deceased animals: hyperaemia of the lung, liver discoloration, acute gastrointestinal inflammation; terminal necropsy was without findings	14 days	Younger Laboratories, 1975; Randall and Bannister, 1990
* Test substance was the commercial product Thiotax Powder, formulated in corn oil.						
Rat	oral	3000	no data	LD_{50}	no data	Vanderbilt, 1975
Rat	oral	3200	no data*	lethal; breathing difficulties, spasms, tremors	no data	Eastman Kodak, 1956
* Propylene glycol served as the vehicle.						
Rat, Sprague-Dawley, male, female	oral	2830	no data*	LD_{50}; reduced food consumption and hypoactivity, weakness, collapse; necropsy of deceased animals: haemorrhage of the lungs, hyperaemia of the liver, acute gastrointestinal inflammation; terminal necropsy was without findings	14 days	Younger Laboratories, 1974
* Test substance was the commercial product Thiotax, formulated in corn oil.						
Rat	oral	1800	no data	LD_{50}	no data	Uniroyal, 1975

Table 2. Acute toxicity of 2-mercaptobenzothiazole						
Species, strain, sex[a)]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat * Oil served as the vehicle.	oral	1680	no data*	LD_{50}	no data	Kowalski and Bassendowska, 1965
Rat, male	oral	> 1600	no data	LD_{50}; weakness, prostration, tremors	no data	Eastman Kodak, 1979, 1980
Rat, Sprague-Dawley, female * Corn oil served as the vehicle.	oral	30, 100, 300, 1000, 3000 and 10000	no data*	mortality 0/1 up to and including 3000 mg, 1/1 at 10000 mg, the latter being the only dose at which weakness, prostration, tremors, convulsions, rapid breathing and salivation occurred and necropsy revealed red lungs	14 days	Industrial Bio-Test, 1977 a
Rat, albino	oral	1000–5500	no data	not lethal; dose-dependent impairment of locomotion, accelerated breathing from 5000 mg	7 days	Litvinchuk, 1963
Rat, domestic Norway	oral	500	no data	mortality: 0/2	4 to 7 days	Dieke et al., 1947
Rat, wild Norway	oral	100	no data	mortality: 0/3	4 to 7 days	Dieke et al., 1947
Mouse, Swiss albino	oral	5000	no data	referred to by the investigators as LD_{50}; mortality: 1/5 at the highest test dose of 5120 mg/kg body weight, 0/5 at the lower dose levels of 3560 and 1280 mg/kg body weight; terminal necropsy was without findings	7 days	Arthur D. Little Inc., 1977
Mouse, albino	oral	3153	technical grade	LD_{50}; convulsions	no data	Litvinchuk, 1963
Mouse, Slc:ddY, male * Test substance was the commercial product Nokuseller M, formulated in olive oil.	oral	3140	technical grade*	LD_{50}; prone position, lacrimation and salivation, tremors, convulsions; necropsy of the animals which died and those which survived to the end of the study was without findings	7 days	Hasegawa et al., 1989; Ogawa et al., 1989 a, b
Mouse, albino	oral	3110	chemically pure	LD_{50}; convulsions	no data	Litvinchuk, 1963
Mouse, ddY, female * Olive oil served as the vehicle.	oral	3080	no data*	LD_{50}; hypoactivity, convulsions; necropsy of the animals which died and those which survived to the end of the study was without findings	14 days	Hasegawa et al., 1989
Mouse, male * Test substance was the purified commercial product Rotax, formulated in carboxymethylcellulose and physiological saline solution.	oral	2000	purified*	LD_{50}; peripheral vasodilation, salivation, convulsions	7 days	Guess and O'Leary, 1969
Mouse	oral	1851	no data	LD_{50}	no data	Vanderbilt, 1975
Mouse * Sunflower oil served as the vehicle.	oral	1800	no data*	LD_{50}; restlessness, impaired motor co-ordination, convulsions, liver alterations	no data	Vorob'eva and Mezentseva, 1962
Mouse, male	oral	> 1600	no data	LD_{50}; weakness, prostration, tremors	no data	Eastman Kodak, 1979, 1980

Table 2. Acute toxicity of 2-mercaptobenzothiazole						
Species, strain, sex[a)]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Mouse	oral	1600	no data*	lethal; breathing difficulties, spasms, tremors	no data	Eastman Kodak, 1956
* Propylene glycol served as the vehicle.						
Mouse, Slc:ddY, male	oral	1558	technical grade*	LD_{50}; prone position, lacrimation and salivation, tremors, convulsions	7 days	Ogawa et al., 1989 a, b
* Test substance was the commercial product Nokuseller M, formulated in gum arabic.						
Mouse, Slc:ddY, female	oral	1490	technical grade*	LD_{50}; prone position, lacrimation and salivation, tremors, convulsions	7 days	Ogawa et al., 1989 a, b
* Test substance was the commercial product Nokuseller M, formulated in gum arabic.						
Mouse, male	oral	931	purified*	maximum tolerated dose	7 days	Guess and O'Leary, 1969
* Test substance was the purified commercial product Rotax, formulated in carboxymethylcellulose and physiological saline solution.						
Rabbit	oral	5000–10000*	no data	mortality was 0/1 after administration of 5000, 6250 and 7500 mg and 1/1 after administration of 8750 and 10000 mg	7 days	Scientific Associates, 1956
* Split into 2 doses given on 2 consecutive days.						
Rabbit	oral	7500–8750	no data	LD_{50}	no data	Scientific Associates, 1974
Rabbit	oral	2000 once or 200 daily for 6 days	no data	no findings (mortality, clinical signs, haematology)	14 days	Litvinchuk, 1963
Rabbit, New Zealand, male, female	dermal	> 7940 (24-hour semi-occlusive exposure of the depilated skin)	97.4%*	LD_{50}; mortality: 0/2; temporary reductions in food consumption and activity; terminal necropsy was without findings	14 days	Younger Laboratories, 1974, 1975; Randall and Bannister, 1990
* Test substances were the commercial products Thiotax and Thiotax Powder, both formulated in corn oil. The purity was taken from the publication by Randall and Bannister (1990) and presumably refers only to Thiotax Powder, as does the oral LD_{50} they reported for the rat.						
Rabbit, New Zealand, male	dermal	300, 1000 or 3000 (aqueous slurry, 24-hour occlusive exposure of the depilated dorsal skin)	no data	mortality was 0/1 at all levels; at 1000 and 3000 mg there was mild erythema and oedema formation, slight desquamation after 7 and 14 days; terminal necropsy was without remarkable findings	14 days	Industrial Bio-Test, 1977 c
Guinea pig	dermal	> 1000	no data	LD_{50}; no signs of absorption through the skin	no data	Eastman Kodak, 1979, 1980
Rat, Charles River, male, female	inhalation (4 hours)	> 1270*	no data	LC_{50}; mortality: 0/10; short-lasting ptosis and hypoactivity; terminal necropsy was without findings	14 days	Industrial Bio-Test, 1977 b
* Heated to 50 °C, fractions of airborne particles < 5 and 10 µm were 78.2 and 10.4%, respectively; presumably represents maximum attainable concentration at 50 °C.						

Table 2. Acute toxicity of 2-mercaptobenzothiazole						
Species, strain, sex[a)]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat, male	inhalation (7 hours)	> ca. 715* (104.4 ppm)	no data*	LC_{50}; mortality: 0/5; no clinical signs of toxicity; terminal necropsy: liver and kidney changes (no precise details)	14 days	Dow, 1961
* Test substance was the commercial product Captax, heated to 40 °C. According to the investigators, the animals were exposed to saturated atmosphere.						
Rat	intraperitoneal	400	no data	lethal; breathing difficulties, spasms, tremors	no data	Eastman Kodak, 1956
Rat	intraperitoneal	300	no data*	LD_{50}	no data	Kowalski and Bassendowska, 1965
* Oil served as the vehicle.						
Rat	intraperitoneal	200–400	no data	LD_{50}	no data	Eastman Kodak, 1980
Mouse, ddY, male	intraperitoneal	334.5–669 (2–4 mmol)	no data	LD_{50}	no data	Shinoda et al., 1974
Mouse, male	intraperitoneal	437	purified*	LD_{50}; peripheral vasodilation, salivation, convulsions	7 days	Guess and O'Leary, 1969
* Test substance was the purified commercial product Rotax, formulated in cottonseed oil.						
Mouse	intraperitoneal	400	no data	lethal; breathing difficulties, spasms, tremors	no data	Eastman Kodak, 1956
Mouse	intraperitoneal	200–400	no data	LD_{50}	no data	Eastman Kodak, 1980
Mouse, male	intraperitoneal	305	purified*	maximum tolerated dose	7 days	Guess and O'Leary, 1969
* Test substance was the commercial product Rotax, formulated in cottonseed oil.						
Mouse, Carworth Farms, male	intraperitoneal	> 300	no data*	LD_{50}	7 days	USAF, 1962
* Carboxymethylcellulose served as the vehicle.						
Mouse, Carworth Farms, male	intraperitoneal	150–200	no data*	LD_{50}	7 days	USAF, 1962
* Water and sodium hydroxide served as the vehicle.						
Mouse, CD1, 2 males, 2 females/dose	intraperitoneal	16.6–1666.6 (given twice at an interval of 24 hours)	98.1%	16.6: without findings; 50.0: reduced muscle tone; 166.6: reduced muscle tone; 500.0: females: mortality 2/2 within 4 hours after the first administration, males: reduced muscle tone, reduced activity and ptosis; 1666.6: mortality 4/4 immediately after the first administration	2 days	Pharmakon Research, 1984 c
Dose-finding study for a micronucleus test, see Section 7.6.2.						
[a)] where specified						

End of Table 2

Beginning of Table 3

Table 3. Subacute toxicity of 2-mercaptobenzothiazole

Species, number/group, regimen	Dose (mg/kg b.w.)	Mortality	Clinical signs	Pathological/histopathological changes	Clinical chemistry/haematology findings	References
Sprague-Dawley rat, male, female, daily oral dietary administration for 4 weeks	no information on any controls which may have been included					Monsanto, year not given
	ca. 357	no effects	no effects	no details of such studies given*	no details of such studies given*	
	ca. 714	no effects	no effects			
	ca. 1071	no effects	reduced body weight gain and feed consumption (males)			
	ca. 1429	no effects	reduced body weight gain and feed consumption			
	ca. 1786	no effects	reduced body weight gain and feed consumption			
* The study is accessible only as a citation in the secondary literature (EC, 1996 a) which gives no details of the study design or the parameters investigated. Dose levels of 5000, 10000, 15000, 20000 and 25000 ppm were administered in the feed.						
F344/N rat, 5 males and 5 females/dose, dosed by oral gavage, 12 doses in 16 days	control (corn oil)					NTP, 1988
	156	0/10	no effects	no macroscopic findings	not studied	
	313	1/10*	no effects	no macroscopic findings	not studied	
	625	2/10*	no effects	no macroscopic findings	not studied	
	1250	0/10	no effects	no macroscopic findings	not studied	
	2500	0/10	reduced body weight gain	no macroscopic findings	not studied	
* gavage error The test substance was administered as the commercial product Captax, 96% pure, in a dose-finding study for a carcinogenicity study carried out as part of the U.S. NTP; histological examination was performed only on the control and top dose groups.						
Rat, 5 animals/dose, oral administration in the feed for 11 days	Controls					Eastman Kodak, 1979, 1980
	91	0/5	no effects	no effects	no effects	
	866	0/5	reduced body weight and feed consumption	increased relative and absolute liver weights without pathological or histopathological correlates	no effects	
Concentrations of 1.5 and 1% were administered in the feed. The conversion to mg/kg body weight is in accordance with the data given by the investigators. Haematology and clinical chemistry parameters studied included haemoglobin, haematocrit, leukocyte and differential blood counts, the activity levels of alanine and aspartate aminotransferase, lactate dehydrogenase and alkaline phosphatase, and blood urea nitrogen and glucose levels; organ weights were determined only for the liver and kidney. The purity of the 2-mercaptobenzothiazole used was not specified.						

Table 3. Subacute toxicity of 2-mercaptobenzothiazole

Species, number/group, regimen	Dose (mg/kg b.w.)	Mortality	Clinical signs	Pathological/histopathological changes	Clinical chemistry/haematology findings	References
B6C3F1 mouse, 5 males and 5 females/dose, dosed by oral gavage, 12 doses in 16 days	control (corn oil)					NTP, 1988
	188	0/10	no effects	no macroscopic findings	not studied	
	375	0/10	no effects	no macroscopic findings	not studied	
	750	0/10	no effects	no macroscopic findings	not studied	
	1500	0/5 M, 4/5 F	lethargy, prostration	no macroscopic findings	not studied	
	3000	4/5 M, 5/5 F	lethargy, prostration	no macroscopic findings	not studied	
The test substance was administered as the commercial product Captax, 96% pure, in a dose-finding study for a carcinogenicity study carried out as part of the U.S. NTP; no histology. The study represents a repeat study of a dose-finding study with dose levels of 156, 313, 625, 1250 and 2500 mg/kg b.w., which was not evaluated due to a very large number of gavage errors. No reasons were given why the doses administered in the repeat study were different from those used in the first study.						
Albino rat, 10 animals, inhalation exposure, 2 hours daily for 15 days (no further details)	Controls 350–400 mg/m³		reduced body weight gain, disturbances of balance, no increase in oxygen consumption, no evidence of changes in the nervous system	no macroscopic findings; histology revealed thickening of the interalveolar septa	not studied	Vorob'eva and Mezentseva, 1962
Mouse, 10 males/dose, intraperitoneal injection, daily for 1 week	Controls (cottonseed oil or physiological saline)					Guess and O'Leary, 1969
	55	no effects	no effects	no macroscopic findings; no histology was performed	not studied	
	110	no effects	prolongation of hexobarbital sleeping time*	liver: necrosis, cloudy swelling, fatty degeneration, changes in the cell nuclei, inflammation; kidney: cloudy swelling of the renal tubules; the lungs, heart, thyroid gland and testes were without findings	not studied	
* The groups dosed with 2-mercaptobenzothiazole in physiological saline solution were given a single 75 mg/kg b.w. dose of sodium hexobarbital to determine hexobarbital sleeping time. The test substance used was the purified commercial product Rotax.						

M males
F females
b.w. body weight

End of Table 3

Beginning of Table 4

Table 4. Skin irritancy of 2-mercaptobenzothiazole

Species	Guideline and/or dose, mode, duration[a)]	Findings	Reversibility	Evaluation (by the investigators)	Reference
Rabbit	500 mg made into an aqueous slurry, 24-hour semi-occlusive application to the depilated intact and scarified skin	no findings (4 hours to 7 days after application)	–	not irritating (irritation index 0.0/8.0)*	Younger Laboratories, 1974, 1975; Randall and Bannister, 1990
* In accordance with the Federal Hazardous Substances Act, 21 CFR, § 191.11 (1964). Test substances were the commercial products Thiotax and Thiotax Powder, 97.4% pure (Randall and Bannister (1990)), but this detail probably only refers to Thiotax Powder, as does the mucous membrane irritation reported by those investigators.					
Rabbit	500 mg mixed with 0.5 ml water, 24-hour occlusive application to the intact depilated dorsal skin	no findings (24 and 72 hours after application)	–	not irritating	Arthur D. Little Inc., 1977
The purity of the 2-mercaptobenzothiazole used was not specified.					
Rabbit	undiluted chemical was applied 10 times to the intact and 3 times to the abraded abdominal skin; a 10% solution in Dowanol DPM was applied 10 times to the intact skin of the ear and the intact abdominal skin and 3 times to the abraded abdominal skin	slight irritation, largely independent of the mode of administration, was associated with slight hyperaemia and slight exfoliation	all findings were reversible within 21 days	mildly irritating	Dow, 1961
The purity of the 2-mercaptobenzothiazole used was not specified.					
Rabbit	intradermal irritation	mild irritation	no data	mildly irritating	Guess and O'Leary, 1969
Carboxymethylcellulose-saline suspensions and cottonseed suspensions containing 0.5, 1, 2 or 4% 2-mercaptobenzothiazole (as the purified commercial product Rotax, purity not specified) were intradermally injected at 4 sites each into the dorsal skin of 4 animals. Visualisation of the area and evaluation of the intensity of irritation was accomplished within 30 minutes with the aid of a 1% trypan blue suspension administered via the marginal ear vein at 1 ml/kg. At 24 hours after intradermal administration, the degree of irritation (erythema, oedema, necrosis) was evaluated. At 48 hours after treatment, the animals were sacrificed, and tissue sections were taken from the injection sites for microscopic examination. 2-Mercaptobenzothiazole caused irritation only when given as a 4% oil suspension. The irritation was classed as mild and transitory and was less than that shown by a 20% ethanol solution (positive control). Histologically, mild inflammation was noted at 24 hours after injection of the 4% suspension in oil. Histological examination at 48 hours after administration was without findings.					
Rabbit	Effect on the healing of scarified skin	no findings	–	–	Guess and O'Leary, 1969
The shaven backs of 4 New Zealand rabbits were swabbed with 70% alcohol, and 4 superficial incisions per animal were made with a scalpel (1 cm long, 2 mm deep and 0.5 cm apart). To the entire area of about 1 cm x 2 cm² oil or aqueous suspensions of 2-mercaptobenzothiazole (the purified commercial product Rotax, purity not specified) were applied at concentrations of 0.5, 1, 2 and 4%. The application sites were observed daily for rate of erythema, healing, scar formation and other adverse effects. 2-Mercaptobenzothiazole was not observed to affect the normal healing of the incisions. Hair growth and total healing time were comparable with the control in all cases.					
Rabbit	2–10% aqueous suspensions injected subcutaneously	no findings	–	no data	Litvinchuk, 1963
The purity of the 2-mercaptobenzothiazole used was not specified.					
Guinea pig	watery paste	no findings (24 hours after application)	–	no data	Du Pont, 1948

Table 4. Skin irritancy of 2-mercaptobenzothiazole					
Species	Guideline and/or dose, mode, duration[a)]	Findings	Reversibility	Evaluation (by the investigators)	Reference
Guinea pig	10% formulation in acetone and corn oil, 24-hour dermal exposure	mild irritation	no data	no data	Eastman Kodak, 1956
The purity of the 2-mercaptobenzothiazole used was not specified.					
Guinea pig	occlusive exposure	mild irritation	no data	mildly irritating	Eastman Kodak, 1979, 1980
The purity of the 2-mercaptobenzothiazole used was not specified.					
Guinea pig	open, repeated skin application for 10 days	showed exacerbation of irritation in 2/5 animals (probably in response to single occlusive application, see above)	no data	no data	Eastman Kodak, 1979, 1980
The purity of the 2-mercaptobenzothiazole used was not specified.					
[a)] where specified					

End of Table 4

Table 5. Mucous membrane effects of 2-mercaptobenzothiazole					
Species	Guideline and/or dose, mode, duration[a)]	Findings	Reversibility	Evaluation (by the investigators)	Reference
Rabbit	100 mg mixed with 0.1 ml water, eyes unwashed	iritis and conjunctivitis in 4/4 eyes assessed, normal cornea	iritis reversible within 7 days, conjunctivitis (score 1 according to Draize) persisting in 2/4 animals	irritating	Arthur D. Little Inc., 1977
The purity of the 2-mercaptobenzothiazole used was not specified.					
Rabbit	100 mg as a powder, eyes probably rinsed after 24 hours	mild irritation with discharge and erythema of the conjunctivae	reversible within 48 hours	not irritating (irritation index 1.3/110)*	Younger Laboratories, 1974
* In accordance with the Federal Hazardous Substances Act, 21 CFR, § 191.12 (1964). Test substance was the commercial product Thiotax Powder, purity not specified.					
Rabbit	100 mg as a powder, eyes probably rinsed after 24 hours	mild to moderate irritation with discharge and erythema of the conjunctivae	reversible within 72 hours	mildly irritating (irritation index 3.2/110)*	Younger Laboratories, 1975; Randall and Bannister, 1990
* In accordance with the Federal Hazardous Substances Act, 21 CFR, § 191.12 (1964). Randall and Bannister (1990) evaluated the effect as practically not irritating. Test substance was the commercial product Thiotax Powder, 97.4% pure.					
Rabbit	100 mg undiluted, eyes unwashed, scored according to the Draize method	iritis and conjunctivitis in 3/3 animals, corneal alterations in 1/3 animals	reversible within 72 hours	mildly irritating (irritation index 18.3/110)	Industrial Bio-Test, 1977 d
The purity of the 2-mercaptobenzothiazole used was not specified.					
Rabbit	undiluted chemical and a 10% suspension in propylene glycol, eyes washed and unwashed	slight irritation with slight to moderate pain reaction and slight conjunctivitis	reversible within 24 and 48 hours (undiluted and diluted chemical, respectively)	very slightly irritating	Dow, 1961
The purity of the 2-mercaptobenzothiazole used was not specified.					
Rabbit	2–10% aqueous suspensions	no findings	no findings	not irritating	Litvinchuk, 1963
Rabbit	no information	slight irritation in 3/3 animals, no alterations of the adnexa or cornea	no information	mildly irritating	Eastman Kodak, 1979, 1980
The purity of the 2-mercaptobenzothiazole used was not specified.					
[a)] where specified					

Beginning of Table 6

Table 6. Sensitising potential of 2-mercaptobenzothiazole in animal studies

Species, type of study	Induction	Adjuvant	Challenge	Animals with positive reactions	Evaluation by the investigators	Reference
Guinea pig, Magnusson and Kligman maximisation test	0.4% as a single intradermal injection and 10% applied dermally, 48-hour occlusive exposure 7 days after dermal induction (both concentrations moderately irritating)	Freund's adjuvant together with intradermal induction	10% (maximum non-irritant concentration) applied dermally, 24-hour occlusive exposure 14 days after dermal induction, repeated 3 times (once weekly)	6/10 (time of assessment not specified)	moderately sensitising	Goodwin et al., 1981
When the test was repeated with intradermal induction concentrations of 0.4, 0.2 and 0.1% but otherwise using identical testing procedures, the response depended on the induction concentration employed, with positive reactions to the challenge treatment being shown by 6/10, 1/10 (equivocal) and 0/10 animals, respectively. The purity of the 2-mercaptobenzothiazole used was not specified.						
Dunkin-Hartley guinea pig, Magnusson and Kligman maximisation test	0.4% as a single intradermal injection and 10% applied dermally, 48-hour occlusive exposure 6 to 8 days after intradermal induction	Freund's adjuvant together with intradermal induction	10% applied dermally (maximum non-irritant concentration), 24-hour occlusive exposure 12 to 14 days after dermal induction	80 and 100% (at 24 and 48 hours, respectively, after challenge)	strongly sensitising	Basketter and Scholes, 1992; Basketter et al., 1993; Scholes et al., 1992
2-Mercaptobenzothiazole, 98% pure, was formulated in acetone/polyethylene glycol 400 (70:30 (v/v), dermal application) or acetone/polyethylene glycol 400/physiological saline solution (6:20:74 (v/v), intradermal injection) and administered in the shoulder region (induction) or on the flank (challenge). The test was carried out in parallel studies at two laboratories.						
Mixed-breed guinea pig, Magnusson and Kligman maximisation test	single intradermal injection, sodium lauryl sulphate applied dermally (8 days after intradermal induction), dermal induction, 48 hours, 9 days after intradermal induction	Freund's adjuvant together with intradermal induction	patch application 14 days after dermal induction	5/12 (24 to 144 hours after challenge)	sensitising	Ziegler et al., 1972
The purity of the 2-mercaptobenzothiazole used and the concentrations administered were not specified.						
Hartley guinea pig, Magnusson and Kligman maximisation test	1% as a single intradermal injection, sodium lauryl sulphate applied dermally (6 days after intradermal induction), 5% applied dermally, 48-hour occlusive exposure 7 days after intradermal induction	Freund's adjuvant together with intradermal induction	0.1% applied dermally, 24-hour occlusive exposure 14 days after dermal induction	5/5 (1 and 24 hours after challenge)	sensitising	Kaniwa et al., 1990 a, 1992
No data were given on the purity of 2-mercaptobenzothiazole, which was formulated in olive oil, petrolatum and acetone for intradermal induction, dermal induction and challenge, respectively. Further studies by the same investigators demonstrated that the number of animals showing a positive response depended on the concentrations of 2-mercaptobenzothiazole used for induction and those used for challenge (Nakamura et al., 1994).						
Hartley guinea pig, Magnusson and Kligman maximisation test	no information	no information	no information	97% (24 and 48 hours after challenge)	sensitising	Trimmer and Freeman, 1988
The purity of the 2-mercaptobenzothiazole used was not specified.						

Table 6. Sensitising potential of 2-mercaptobenzothiazole in animal studies

Species, type of study	Induction	Adjuvant	Challenge	Animals with positive reactions	Evaluation by the investigators	Reference
Hartley guinea pig, Magnusson and Kligman maximisation test	1% as a single intradermal injection and 25% applied dermally, 48-hour occlusive exposure one week after intradermal induction	Freund's adjuvant together with intradermal induction	15% applied dermally, 48-hour occlusive exposure 14 days after dermal induction	8/20 (24 hours after challenge)	moderately sensitising	Magnusson and Kligman, 1969, 1970
The purity of the 2-mercaptobenzothiazole used was not specified. When two groups of 20 animals underwent 2-mercaptobenzothiazole induction, one intradermally (1%) and the other dermally (25%), only one animal/group showed a positive response to the challenge treatment.						
Albino guinea pig, Magnusson and Kligman maximisation test	test group 1: 3% applied to the skin daily for 3 weeks; test groups 2: single intradermal heparin injection, followed by 5% applied dermally 8 times in 3 weeks; test group 3: 1000 µg as a single intradermal injection into the ear; test group 4: 3% applied to the skin daily for 3 weeks and 100 µg injected into the skin daily for 3 weeks	Freund's adjuvant together with the intradermal inductions	750 µg applied dermally 11 to 14 days after induction	6/36, 6/40, 4/40 and 18/42 in the 4 respective test groups	sensitising	Barlogova and Stolcova, 1984
No data were given on the purity of the technical-grade 2-mercaptobenzothiazole, which was used as a formulation in acetone. An additional experiment was able to demonstrate cross reactions to 2-mercaptobenzimidazole.						
Guinea pig, modified Draize test	0.75% as a single intradermal injection	without adjuvant	0.3% as an intradermal injection (marginally irritant concentration) and 10% applied dermally (maximum non-irritant concentration) on opposite flanks 14 days after induction	0/10 (24 hours after challenge)	not sensitising	Goodwin et al., 1981
The purity of the 2-mercaptobenzothiazole used was not specified.						
Guinea pig, Single Injection Adjuvant Test (SIAT)	0.4% as a single intradermal injection (moderately irritant concentration)	Freund's adjuvant was used as the vehicle for induction	10% applied dermally (maximum non-irritant concentration), 6-hour occlusive exposure 12 to 14 days after induction, repeated 3 times (once weekly)	0/10 (18 and 42 hours after challenge)	not sensitising	Goodwin et al., 1981
When the test was repeated using additional patch induction (10%) but otherwise identical testing procedures, 1/10 test animals showed equivocally positive responses to the challenge treatment. The purity of the 2-mercaptobenzothiazole used was not specified.						
Hartley guinea pig, Landsteiner-Draize test	0.1% repeated intradermal injections (10 in 3 weeks)	without adjuvant	0.1% as an intradermal injection, 14 days after the last induction	6/6 (24 hours after challenge)	sensitising	Cannon Laboratories, 1977
No data were given on the purity of the 2-mercaptobenzothiazole, which was formulated in physiological saline solution.						

Table 6. Sensitising potential of 2-mercaptobenzothiazole in animal studies						
Species, type of study	Induction	Adjuvant	Challenge	Animals with positive reactions	Evaluation by the investigators	Reference
Hartley guinea pig, Landsteiner-Draize test	0.1% repeated intradermal injections (10 in 3 weeks)	without adjuvant	0.1% as an intradermal injection, 14 days after the last induction	0/20	not sensitising	Magnusson and Kligman, 1969, 1970
The purity of the 2-mercaptobenzothiazole used was not specified.						
Pirbright White guinea pig, optimisation test	0.1% repeated intradermal injections (9 in 3 weeks)	Freund's adjuvant in the 2nd and 3rd weeks of induction	0.1% as an intradermal injection 14 days after the last induction, 5% applied dermally (maximum non-irritant concentration), 24-hour occlusive exposure 14 days after the last intradermal challenge	19/20 (intradermal and dermal challenge, 24 hours after the respective challenge)	strongly sensitising	Maurer et al., 1979
2-Mercaptobenzothiazole p.a. was administered as a formulation in 30% aqueous propylene glycol or Freund's adjuvant.						
Guinea pig, Brulos patch test	0.5 g applied dermally, 48-hour occlusive exposure, 10 applications in 4 weeks	Freund's adjuvant administered once in the 1st and the 2nd week of induction	1% in petrolatum, one week after the last induction	50% (1 to 72 hours after challenge)	moderately sensitising	Bourrinet et al., 1979
The purity of the 2-mercaptobenzothiazole used was not specified.						
Hartley guinea pig, Buehler patch test	no information	no information	no information	29 and 53% at the 1st and 2nd challenge (24 or 48 hours after the respective challenge)	sensitising	Trimmer and Freeman, 1988
The purity of the 2-mercaptobenzothiazole used was not specified.						
Dunkin-Hartley guinea pig, Buehler patch test	20% applied dermally (slightly irritating concentration), 6-hour occlusive exposure, once weekly for 3 weeks	no information	10% applied dermally (maximum non-irritant concentration), 6-hour occlusive exposure 12 to 14 days after dermal induction	20 and 55% (at 24 and 48 hours, respectively, after challenge)	sensitising	Basketter et al., 1993
2-Mercaptobenzothiazole, 98% pure, was formulated in acetone/polyethylene glycol 400 (70:30 (v/v)) and applied to the depilated skin of the shoulder (induction) or flank (challenge). The test was carried out in parallel studies at two laboratories.						
Hartley guinea pig, Buehler patch test	5% applied dermally (concentration causing minimal irritation), 24-hour occlusive exposure, 3 times weekly for 2 weeks	no information	0.1, 0.5 and 2% applied dermally (2% constituting the maximum non-irritant concentration), 24-hour occlusive exposure 14 days after induction	7/10, 2/10 and 0/10 in the 2, 0.5 and 0.1% groups, respectively (24 hours after challenge)	sensitising	Wang and Suskind, 1984, 1986, 1988
The purity of the 2-mercaptobenzothiazole used was not specified. White petrolatum was used as the vehicle. In a cross-sensitisation study in the 2% dose group, when inspected 7 days after the challenge with 2-mercaptobenzothiazole, 3 of the 7 of the animals with a positive response to 2-mercaptobenzothiazole also showed a positive reaction to the 2% formulation of morpholinylmercaptobenzothiazole, and all animals sensitised by morpholinylmercaptobenzothiazole also responded to 2-mercaptobenzothiazole. Cross-sensitisation to morpholine and 4,4'-dithiodimorpholine was not noted.						

Table 6. Sensitising potential of 2-mercaptobenzothiazole in animal studies

Species, type of study	Induction	Adjuvant	Challenge	Animals with positive reactions	Evaluation by the investigators	Reference
Guinea pig, patch test	0.5 M applied occlusively to the skin	no information	0.5 and 0.05 M	0/12	not sensitising	Kantoh et al., 1985
The publication, essentially written in Japanese, provides no further details.						
Guinea pig, skin sensitisation test	no information	no information	no information	no findings	not sensitising	Eastman Kodak, 1956
No further details.						
Guinea pig, skin sensitisation test	no information	no information	no information	0/5	not sensitising	Eastman Kodak, 1979, 1980
No further details.						
CBA/Ca mouse, local lymph node assay	25 µl of a 10, 25 or 50% formulation in dimethylformamide was applied dermally once daily for 3 days; 4 to 5 days after the first treatment 20 µCi ^{3}HTdR was given i.v.; 5 hours later the animals were sacrificed and proliferation of the auricular lymph node cells was determined by measuring ^{3}HTdR incorporation	without adjuvant	not applicable	dose-dependently increased proliferation of lymph node cells relative to control	strongly sensitising	Basketter and Scholes, 1992; Basketter et al., 1993, 1994; Scholes et al., 1992
Parallel studies in 4 independent laboratories. The purity of the 2-mercaptobenzothiazole used was not specified.						
CBA/Ca mouse, local lymph node assay	a 10, 25 or 50% formulation in dimethylformamide was applied dermally once daily for 3 days; 5 days after the first treatment 20 µCi ^{3}HTdR was given i.v.; 5 hours later the animals were sacrificed and proliferation of the auricular lymph node cells was determined by measuring ^{3}HTdR incorporation	without adjuvant	not applicable	increased proliferation of lymph node cells relative to control	strongly sensitising	Corning Hazleton, 1996
The 2-mercaptobenzothiazole used was 98% pure.						
BALB/c mouse, local lymph node assay	25 µl of a 2.5, 5 or 10% formulation was applied dermally for 3 days; the animals were sacrificed one day later and proliferation of the auricular lymph node cells was determined by measuring ^{3}HTdR incorporation in vitro	without adjuvant	not applicable	dose-dependently increased proliferation of lymph node cells relative to control	sensitising	Ikarashi et al., 1993 a, b

Table 6. Sensitising potential of 2-mercaptobenzothiazole in animal studies

Species, type of study	Induction	Adjuvant	Challenge	Animals with positive reactions	Evaluation by the investigators	Reference
No data were given on the purity of the technical-grade 2-mercaptobenzothiazole, which was formulated in acetone-olive oil (4:1) and applied to the skin of the ear.						
BALB/c mouse, optimised local lymph node assay	25 µl of a 0.2 or 2% formulation was given as a single intradermal injection into the abdominal skin; after 5 days a 10% formulation was applied dermally for 3 days; the animals were sacrificed one day after the final dermal induction, and proliferation of the auricular lymph node cells was determined by measuring ^{3}HTdR incorporation in vitro	Freund's adjuvant was used as the vehicle for intradermal induction	not applicable	depending on the concentration of the formulation used for intradermal induction there was increased proliferation of lymph node cells relative to the control and the above-mentioned test (Ikarashi et al., 1993 a, b) without Freund's adjuvant	sensitising	Ikarashi et al., 1993 b 1993 b
No data were given on the purity of the 2-mercaptobenzothiazole, which was formulated in acetone-olive oil (4:1) and applied to the skin of the ear for dermal induction.						
C57BL/10 or DBA/2 mouse, popliteal lymph node assay	1 mg/animal was injected into the right hind footpad; animals were sacrificed after 7 days and the popliteal lymph nodes weighed	without adjuvant	not applicable	lymph node weights of the treated right hind legs were increased relative to the untreated left hind legs and the untreated controls in C57BL/10 mice, whilst in DBA/2 mice lymph node weights were increased only relative to the untreated legs	equivocal*	Kammüller et al., 1989
* According to the description given in the text the findings suggest a sensitising effect. However, in the tabular presentation the results were nonsignificant. No data were given on the purity of the 2-mercaptobenzothiazole, which was formulated in DMSO.						
[a)] where specified ^{3}HTdR [^{3}H]-methyl thymidine						

End of Table 6

Beginning of Table 7

Table 7. In-vitro genotoxicity tests with 2-mercaptobenzothiazole

Test system	Concentration range tested (µg/ml)	Metabolic activation	Results		Reference
			without metabolic activation	with metabolic activation	
1. Gene mutation					
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538, standard plate incorporation test with an independent repeat study (only TA 98 and TA 1538 + S9 mix)	3–300 µg/ml (–S9), 3–600 µg/ml (+S9)	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Pharmakon Research, 1984 a
The 2-mercaptobenzothiazole used was 98.1% pure.					
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538, standard plate incorporation test	0.1–500 µg/plate, toxicity tested	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Litton Bionetics, 1976
Test substance was the product Bio-76-177 CP 1975 Thiotax, purity not specified.					
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, standard plate incorporation test, 3 parallel assays with an independent repeat	8–200 µg/plate, top concentration toxic	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Crebelli et al., 1984 b, 1985
The 2-mercaptobenzothiazole used was 94% pure (no details of impurities).					
Salmonella/microsome test, Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538, standard plate incorporation test	not specified, toxicity tested	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Rannug et al., 1984
Tests were carried out with technical-grade 2-mercaptobenzothiazole (no details of impurities).					
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, standard plate incorporation test	0.1–100, no data on toxicity	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Goodyear, 1980
Tests were carried out with technical-grade 2-mercaptobenzothiazole (Captax; purity not specified).					
Salmonella/microsome test, *Salmonella typhimurium* TA 97, TA 98, TA 100, TA 102, standard plate incorporation test	1–5000 µg/plate, toxic from 1000 µg	S9 mix (no further details)	negative	negative	BFG, 1984
The purity of the 2-mercaptobenzothiazole used was not specified.					
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100, standard plate incorporation test	not specified, not tested in the toxic range	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Hedenstedt et al., 1981
The purity of the 2-mercaptobenzothiazole used was not specified.					
Salmonella/microsome test, *Salmonella typhimurium* TA 97, TA 98, TA 100, TA 102, preincubation test	1–1000 µg/plate, toxicity tested	S9 mix (no further details)	negative	negative	BFG, 1984
The purity of the 2-mercaptobenzothiazole used was not specified.					

Table 7. In-vitro genotoxicity tests with 2-mercaptobenzothiazole					
Test system	Concentration range tested (µg/ml)	Metabolic activation	Results		Reference
			without metabolic activation	with metabolic activation	
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100, preincubation test with an independent repeat	8–200 µg/plate, toxicity tested	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Crebelli et al., 1984 a
The 2-mercaptobenzothiazole used was 94% pure (no details of impurities).					
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, preincubation test, parallel studies with one or two independent repeats performed at two laboratories	0–10000 µg/plate, toxicity tested	S9 mix from Aroclor 1254-induced rat and hamster liver	negative	negative, TA 98 equivocal*	NTP, 1988 Zeiger et al., 1987, 1990; Zeiger, 1990
The 2-mercaptobenzothiazole used was 96.3% pure (no details of impurities). * For strain TA 98, results were negative in the presence of metabolic activation in one of the two laboratories, while in the second laboratory two sets of 3 separate trials, one set performed with rat liver S9 mix, the other with hamster liver S9 mix, each produced one weakly positive, one equivocal and one negative result.					
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100	0–100 µg/plate, toxicity tested	S9 mix	negative	negative	Yamaguchi et al., 1991
The publication, written in Japanese, provides no further details.					
Salmonella/microsome test, *Salmonella typhimurium* TA 98, TA 100	1–100 µg/plate	S9 mix	negative	negative	Ebringer et al., 1985
The publication, written in Czech, provides no further details.					
Escherichia coli Sd-4-73, induction of streptomycin-independent revertants	no precise details	not tested	negative	not tested	Szybalski, 1958
The purity of the 2-mercaptobenzothiazole used was not specified.					
V79/HPRT test, 6-thioguanine resistance, Chinese hamster lung fibroblasts (V79)	0–300, toxicity tested	not tested	negative	not tested	Donner et al., 1983
The purity of the 2-mercaptobenzothiazole used was not specified.					
CHO/HPRT test, 6-thioguanine resistance, Chinese hamster ovary cells, (CHO-K1-BH4), 2 parallel studies	1–50 µg/ml (–S9), 10–300 µg/ml (+S9), higher concentrations too toxic	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Pharmakon Research, 1984 b
The 2-mercaptobenzothiazole used was 98.1% pure.					

Table 7. In-vitro genotoxicity tests with 2-mercaptobenzothiazole

Test system	Concentration range tested (µg/ml)	Metabolic activation	Results		Reference
			without metabolic activation	with metabolic activation	
L5178Y/TK assay, trifluorothymidine resistance, mouse lymphoma cells (L5178Y/TK), each sample assayed in triplicate with one (–S9) and two (+S9) independent repeat assays	30–150 (–S9), 1.25–20 (+S9), top concentration toxic	S9 mix from Aroclor 1254-induced rat liver	negative	positive or weakly positive*	Myhr et al., 1990; NTP, 1988; Zeiger et al., 1990
The 2-mercaptobenzothiazole used was 96.3% pure (no details of impurities; see Zeiger et al., 1990). * The results from two trials, one with concentration levels ranging from 5 to 16 µg/ml and the other testing levels of 4 to 20 µg/ml, are reported practically identically in the two detailed publications (Myhr et al., 1990; NTP, 1988). Mutant frequencies (MF) showed a more or less concentration-dependent rise in the first of these trials from approx. 35 in the solvent control (ethanol) to a maximum of 104 at 10 µg/ml (approx. 3-fold increase), while in the second trial increases were seen from 39 in solvent control to maximum frequencies of approx. 75 and 72 at the second highest and highest concentration levels of 16 and 20 µg/ml (approx. 1.9- and approx. 1.8-fold increases), respectively. In addition, the NTP (1988) publication contains a table with the raw data from a further trial of concentration levels ranging from 1.25 to 15 µg/ml, in which only the top concentration showed a statistically significant increase in mutant frequency to 130 (approx. 1.6-fold), relative to a value of 79 obtained for the solvent control, whilst Myhr et al. (1990) present the raw data table from a trial, in which test concentrations of 5 to 16 µg/ml were not found to be associated with a statistically significant increase in mutant frequency relative to the solvent control (mutant frequency 45). In summary, given the relatively small increase (1.6- to maximum 3-fold) in mutant frequency relative to controls and only moderate reproducibility and dose-dependency, the outcome of this study was weakly positive rather than positive.					
L5178Y/TK assay, trifluorothymidine or bromodeoxyuridine resistance, mouse lymphoma cells (L5178Y/TK), test with three independent repeat assays	1.56–100, top concentrations severely toxic	S9 mix from Aroclor 1254-induced rat liver	negative*	negative*	Litton Bionetics, 1979
Test substance was the product Thiotax BO-78-240, purity not specified. * Small increases in mutant frequencies (maximum 3.1-fold) at some highly toxic concentrations in a total of 4 assays were not reproducible.					
L5178Y/TK assay, mouse lymphoma cells (L5178Y/TK), assay with one (–S9) and two (+S9) independent repeat assays	3.75–150 (–S9), 3.75–120 (+S9), concentration-dependent toxicity	S9 mix from rat liver (no further details)	weakly positive*	weakly positive*	Litton Bionetics, 1985
The purity of the 2-mercaptobenzothiazole used was not specified. * The positive results were only seen in highly toxic concentration ranges (–S9: 1.8- to 8.7-fold increase in mutant frequencies in concentration ranges with relative growth ≤ 10%; + S9: 1.7- to 2.7-fold increase in mutant frequencies in concentration ranges with relative growth between 7 and 20%). The investigators evaluated 2-mercaptobenzothiazole as weakly mutagenic at highly toxic concentration levels, both in the absence and in the presence of S9 mix.					
2. Chromosome damage					
Chromosome aberration, Chinese hamster ovary (CHO) cells, 25 to 100 metaphases examined per concentration	10–30.1 (–S9), 351.8–500.5 and 373.5–450 (+S9), none of the top concentrations were evaluable due to cytotoxicity	S9 mix from Aroclor 1254-induced rat liver	negative	positive	Anderson et al., 1990; NTP, 1988; Zeiger et al., 1990
The 2-mercaptobenzothiazole tested was 96.3% pure (no details of impurities; see Zeiger et al., 1990). As all concentrations caused cell cycle delay, the incubation time as per standard protocol was lengthened.					

Table 7. In-vitro genotoxicity tests with 2-mercaptobenzothiazole

Test system	Concentration range tested (µg/ml)	Metabolic activation	Results		Reference
			without metabolic activation	with metabolic activation	
3. DNA damage					
DNA repair test, *Escherichia coli* WP2, WP2 uvrA	1–100 µg/plate	no information	negative		Ebringer et al., 1985
The publication, written in Czech, provides no further details.					
Saccharomyces cerevisiae D4, induction of tryptophan-independent mutants (mitotic gene conversion), standard plate incorporation test	0.1–500 µg/plate, toxicity tested	S9 mix from Aroclor 1254-induced rat liver	negative	negative	Litton Bionetics, 1976
Test substance was the product Bio-76-177 CP 1975 Thiotax, purity not specified.					
SCE test, Chinese hamster ovary (CHO) cells, 50 metaphases examined per concentration	12.5–24.8 (–S9), 99.2–750 and 351.6–502.3 (+S9), toxicity tested, none of the top concentrations were evaluable as cytotoxicity was too high	S9 mix from Aroclor 1254-induced rat liver	negative	positive or equivocal*	NTP, 1988
The 2-mercaptobenzothiazole used was 96.3 or 96.8% pure (no details of impurities). * Without metabolic activation, 2-mercaptobenzothiazole was negative (only one trial carried out). With metabolic activation, 2-mercaptobenzothiazole was evaluated as positive by the investigators. In the presence of metabolic activation, the first trial showed a concentration-dependent increase in relative sister chromatid exchanges/cell (SCE rate) by approx. 12, 13 and 35% compared with the control. An increase in SCE rate by more than 20% which the investigators evaluated as significant was only observed at the highest test concentration of 501.5 µg/ml in association with cell cycle delay. The cytotoxicity from the comparable concentration of 502.3 µg/ml used in the second trial was too high to permit evaluation. Therefore, the results of the first trial cannot serve as a criterion of activity in this concentration range, not least because the observed cell cycle delay also indicates that the concentrations tested were cytotoxic. If, however, the result for the highest concentration in the first trial is excluded, there is no longer a significant increase in SCE rate, and hence the outcome of the trial must be evaluated as negative. In the second trial, the 3 evaluable concentration levels from 351.6 to 445.3 µg/ml showed concentration-independent increases in SCE rate by approx. 23, 37 and 30% in association with cell cycle delay. Hence, this trial also gave no clearly positive result, because a concentration-dependent increase in SCE rate was a criterion for evaluating the outcome as positive. Another criticisable aspect of data evaluation in this test is that the minimum increase in SCE of 20% over controls, predetermined by the investigators as representing a significant increase, was a very low limit. More recent suggestions regarding the evaluation of SCE tests advocate that the criterion for a clearly positive result must be an at least 2-fold increase in SCE rate (cf. Speit, 1993). Moreover, it can not be precluded that owing to cell cycle delay (harvest time > 34 hours), longer exposure to bromodeoxyuridine contributed to the increase in SCE rate (cf. Anderson et al., 1990). In conclusion, the evaluation of the test results by the investigators must be questioned, and hence, this study should be regarded as not relevant to the assessment of the genotoxic potential of 2-mercaptobenzothiazole.					

Table 7. In-vitro genotoxicity tests with 2-mercaptobenzothiazole

Test system	Concentration range tested (µg/ml)	Metabolic activation	Results		Reference
			without metabolic activation	with metabolic activation	
SCE test, Chinese hamster ovary (CHO) cells, 50 metaphases examined per concentration	0.5–16 (–S9), 5–160 (+S9), toxicity tested	S9 mix from Aroclor 1254-induced rat liver	positive or equivocal*	weakly positive or equivocal*	Anderson et al., 1990; Zeiger et al., 1990
The 2-mercaptobenzothiazole used was 96.3% pure (no details of impurities; see Zeiger et al., 1990). * The test was carried out as part of the U.S. NTP, using standard incubation periods (harvest time 25 to 29 hours), because the above-mentioned test that was evaluated as positive by the investigators was obtained in a study with cell cycle delay (harvest time > 34 hours; NTP, 1988). Discussing their results, the investigators conceded that prolonged exposure to bromodeoxyuridine owing to cell cycle delay could not be excluded and may have contributed to the increases in SCE rates. In the absence of metabolic activation, 2-mercaptobenzothiazole was evaluated as positive in one of two trials, as the intermediate concentrations of 1.6 and 5 µg/ml caused concentration-dependent increases in SCE rates by approx. 21 and approx. 24%, respectively, relative to the controls. The second trial, without metabolic activation, failed to reproduce the increases in SCE rates evaluated as significant in the first trial. The test result of the second trial, without metabolic activation, was evaluated as equivocal, given that relative to the control the SCE rate was increased by approx. 24% at the lowest concentration level of 0.5 µg/ml. No comparable increase was noted in the first trial. In the presence of metabolic activation, the result was evaluated as weakly positive, since with the second highest concentration of 50 µg/ml a concentration-independent increase in SCE rate by approx. 24% was observed, relative to the control (only one trial carried out). For this test, too, it must be pointed out that the minimum increase in SCE of 20% over controls, predetermined by the investigators as representing a significant increase, was a very low limit. More recent suggestions regarding the evaluation of SCE tests advocate that the criterion for a clearly positive result must be an at least 2-fold increase in SCE rate, concentration-dependency of the increases in SEC rates and reproducibility of the results (cf. Speit, 1993). In conclusion, the evaluation of the test results by the investigators must be questioned, and hence, this study should also be regarded as not relevant to the assessment of the genotoxic potential of 2-mercaptobenzothiazole.					
4. Other tests					
Genotoxicity test in bacteria, no further details	no information	no information	negative		JETOC, 1985
Genotoxicity test in *Euglena gracilis* The publication, written in Czech, provides no further details.	100 and 200	no information	negative		Ebringer et al., 1985

End of Table 7

Beginning of Table 10

Table 10. Reproductive toxicity of 2-mercaptobenzothiazole

Type of study, test system	Dose (mg/kg body weight/day or mg/m³)	Parental toxicity	Embryotoxicity/foeto-toxicity	Teratogenicity	Development of offspring	Reference
Teratogenicity/embryotoxicity study, Sprague-Dawley rat, 26 rats/dose, administration by oral gavage on days 6–15 of gestation, sacrifice on day 20 of gestation	control (corn oil)					Springborn Laboratories, 1989 b; Rodwell et al., 1990
	300	no findings	no findings*	no findings	not studied	
	1200	salivation, urine-stained coat, dark material around the mouth	no findings*	no findings	not studied	
	1800	body weight loss, reduced food consumption, salivation, urine-stained coat, dark material around the mouth, decreased activity	no findings*	no findings	not studied	
* Slight, statistically significant increases in postimplantation loss (early resorptions) were seen at the high and low doses but not in the intermediate dose group. They were deemed toxicologically equivocal (top dose) and biologically insignificant (low dose) by the investigators, as the increases lacked dose-dependence and were in the range of historical controls or controls reported in the literature, the values for the control group were unusually low and no corresponding effect was observed in the range-finding study (see below). Study in accordance with the TSCA guideline (EPA, 1985 a, 1987, 1988). The 2-mercaptobenzothiazole used was 98.5 and 98.1% pure (as analysed before and after the study, respectively).						
Teratogenicity/embryotoxicity study, range-finding study, Sprague-Dawley rat, 6 rats/dose, administration by oral gavage on days 6–15 of gestation, sacrifice on day 20 of gestation	control (corn oil)					Springborn Laboratories, 1989 a
	300	no findings	no findings	no findings	not studied	
	600	salivation	no findings	no findings	not studied	
	1000	salivation	no findings	no findings	not studied	
	1500	body weight loss, salivation, urine staining	no findings	no findings	not studied	
	2200	mortality 2/6, body weight loss, salivation, urine staining, dark material around the mouth	no findings	no findings	not studied	
Study in accordance with the TSCA guideline (EPA, 1985 a, 1987, 1988). The 2-mercaptobenzothiazole used was 98.5 and 98.1% pure (as analysed before and after the study, respectively).						
Teratogenicity/embryotoxicity study, New Zealand guinea pig, 20 guinea pigs/dose, administration by oral gavage on days 6–18 of gestation, sacrifice on day 29 of gestation	control (methylcellulose)					Springborn Laboratories, 1989 d; Rodwell et al., 1990
	50	no findings	no findings	no findings	not studied	
	150	no findings	no findings	no findings	not studied	
	300	increase in relative and absolute liver weights, slight but not significant body weight loss	no findings	no findings	not studied	
Study in accordance with the TSCA guideline (EPA, 1985 a, 1987, 1988). The 2-mercaptobenzothiazole used was 98.5 and 98.1% pure (as analysed before and after the study, respectively).						

Table 10. Reproductive toxicity of 2-mercaptobenzothiazole

Type of study, test system	Dose (mg/kg body weight/day or mg/m³)	Parental toxicity	Embryotoxicity/foeto-toxicity	Teratogenicity	Development of offspring	Reference
Teratogenicity/embryotoxicity range-finding study, New Zealand guinea pig, 5 guinea pigs/dose, administration by oral gavage on days 6–18 of gestation, sacrifice on day 29 of gestation	control (methylcellulose)					Springborn Laboratories, 1989 c
	150	depressed body weight gain	reduced foetal weight	no findings	not studied	
	300	depressed body weight gain	reduced foetal weight	no findings	not studied	
	600	mortality 1/6*, 1 female aborted, body weight loss	reduced foetal weight, increase in postimplantation losses	no findings	not studied	
	1000	mortality 3/6*, 1 female aborted	–*	–*	not studied	
	1500	mortality 5/6*, laboured breathing	–*	–*	not studied	
* The animals which died or aborted were found to have morphopathological changes of the stomach, lung and kidney. In the two highest dose groups, no foetuses were available for examination due to high maternal toxicity. Study in accordance with the TSCA guideline (EPA, 1985 a, 1987, 1988). The 2-mercaptobenzothiazole used was 98.5 and 98.1% pure (as analysed before and after the study, respectively).						
Teratogenicity/embryotoxicity study, Sprague-Dawley rat, 10–15 rats/group, intraperitoneal administration on days 1–15 of gestation, sacrifice on day 21 of gestation	control (corn oil)					Hardin et al., 1981
	200 (MTD)*	no findings*	no findings	no findings	not studied	
* The administered dose was that which had been identified as the MTD in initial studies. The MTD was defined as the maximum dose (administered daily for 15 days) at which the animals showed no increased mortality, no marked clinical signs of toxicity and less than a 10% reduction in body weight gain relative to controls during the administration period and the 14-day observation period.						
Teratogenicity/embryotoxicity study with monitoring of postnatal development for 21 days postpartum, ICR mouse, 26–37 mice/group, of which 15–18 were pregnant, oral administration during gestation	control (aqueous gum arabic solution)					Morita et al., 1979
	40	no findings	no findings	no findings	no findings	
	1000	depressed body weight gain	increased number of dead foetuses (early stage, no precise details), reduced birth weight of live pups, delayed ossification	no findings	no findings	
* The purity of the 2-mercaptobenzothiazole used was not specified in the English parts of the publication (abstract, tables), which was written in Japanese.						

Table 10. Reproductive toxicity of 2-mercaptobenzothiazole

Type of study, test system	Dose (mg/kg body weight/day or mg/m³)	Parental toxicity	Embryotoxicity/foeto-toxicity	Teratogenicity	Development of offspring	Reference
Teratogenicity/embryotoxicity studies, BL6 mouse, AKR mouse, C3H mouse, 6–13 mice/group, subcutaneous administration on days 6–14 or 15 of gestation, sacrifice on day 18. or 19 of gestation; test substance was the commercial product Captax (purity not specified)	control (DMSO)					Bionetics Research, 1968 b
	300 (C3H mouse)	increased relative liver weight	no findings	no findings	not studied	
	464 (C3H mouse)	depressed body weight gain, increased relative placental weight	reduced foetal weight and crown-rump length, increased number of foetuses with morphological changes (intestinal displacement, wavy ribs, club foot; no distinction between embryotoxic/foetotoxic effects and teratogenic changes)	reduced foetal weight and crown-rump length, increased number of foetuses with morphological changes (intestinal displacement, wavy ribs, club foot; no distinction between embryotoxic/foetotoxic effects and teratogenic changes)	not studied	
	464 (BL6 mouse, 1st study)	increases in relative liver and placental weights	increased number of foetuses with morphological changes (tongue lesions, microphthalmia; no distinction between embryotoxic/foetotoxic effects and teratogenic changes)	increased number of foetuses with morphological changes (tongue lesions, microphthalmia; no distinction between embryotoxic/foetotoxic effects and teratogenic changes)	not studied	
	464 (BL6 mouse, 2nd study)	increased relative liver weight	no findings	no findings	not studied	
	464 (AKR mouse)	increased relative liver weight	no findings	no findings	not studied	
The investigators discussed the problem that the relevance of these inconsistent findings was unclear.						

Table 10. Reproductive toxicity of 2-mercaptobenzothiazole

Type of study, test system	Dose (mg/kg body weight/day or mg/m³)	Parental toxicity	Embryotoxicity/foeto-toxicity	Teratogenicity	Development of offspring	Reference
Two-generation study, Sprague-Dawley rat, 8 males and 8 females/dose, oral administration in feed from 70 days prior to mating of the F0 rats until scheduled sacrifice of the F0, F1 and F2 rats after weaning and weaning of the offspring at age 28 days; F1 rats received 2-mercaptobenzothiazole in the feed for a minimum of 88 days prior to mating	control (basal diet)					Mercieca et al., 1991; Springborn Laboratories, 1990
	2500 ppm in feed	see below*	no findings	no findings	no relevant reproductive toxicity findings*	
	8750 ppm in feed	see below*	no findings	no findings	no relevant reproductive toxicity findings*	
	15000 ppm in feed	see below*	no findings	no findings	no relevant reproductive toxicity findings*	

* Dose-dependent depression of body weight gain, which in some cases was only of short duration, was seen in all generations at all dose levels in association with at least temporary reduction in food consumption in the mid and top dose groups. Body weight gain was depressed in the mid and top dose F1 animals from lactation day 7 and in the F2 animals of all dose groups from lactation day 14. Histopathological kidney changes were observed in the parental F0 and F1 animals of the mid and top dose groups in the form of brown pigment in the lumen and the epithelial cells of the proximal convoluted tubules (more frequent in males than in females). In all dose groups, only the males had cortical tubular basophilia and $\alpha_{2\mu}$-globulin inclusions, which in the mid and top dose groups correlated with an increase in relative and absolute kidney weights. Histopathological liver changes occurred in the form of parenchymal hepatocyte hypertrophy in the parental F1 males and females of the mid and top dose groups in association with increased absolute liver weights in the males of the mid and top dose groups and the top dose females, and increased relative liver weights in the males of all dose groups and the females of the mid and top dose groups. All parameters related to reproductive toxicity (mating behaviour, fertility, gestation length, litter size and viability, pup weight at birth, macroscopic appearance of the reproductive organs of all adults and the histopathology of the reproductive organs of the adults treated with 15000 ppm) were normal. According to the summarising evaluation of the study by the investigators, the F0, F1 and F2 groups were observed to have minimal to mild signs of 2-mercaptobenzothiazole toxicity, without there being any indications of a reproductive toxicity potential.
Study in accordance with the TSCA guideline (EPA, 1985 a, 1987, 1988). The 2-mercaptobenzothiazole used was 98.2 and 98.5% pure. Intake of 2-mercaptobenzothiazole in the 15000 ppm dose group corresponded to the following doses in mg/kg body weight/day: approx. 778 to 1328 and 779 to 2633 in F0 males and parental F1 males, respectively, and 745 to 1760 and 980 to 1770 in F0 females and parental F1 females (the females' last lactation weeks were not taken into account as the offspring were also already exposed to 2-mercaptobenzothiazole in the feed).

Table 10. Reproductive toxicity of 2-mercaptobenzothiazole						
Type of study, test system	Dose (mg/kg body weight/day or mg/m³)	Parental toxicity	Embryotoxicity/foeto-toxicity	Teratogenicity	Development of offspring	Reference
Preliminary study to the above-mentioned two-generation study, Sprague-Dawley rat, 10 females/group, oral administration in the F0 females' feed from day 0 of gestation to day 21 of lactation and in the F1 rats' feed up to age 35 days	control (basal diet) 15000 ppm in feed	reduced body weight gain and feed consumption	no findings	no findings (only externally visible changes were noted)	reduced body weight gain during lactation and after weaning in association with reduced food consumption after weaning	Springborn Laboratories, 1989 f
	15000 ppm in feed initially until day 7 of lactation, then 10000 ppm until day 14 of lactation and subsequently 5000 ppm until the F1 animals were 35 days old	reduced body weight gain and feed consumption, increased body weight gain relative to control upon dose reduction	no findings	no findings (only externally visible changes were noted)	reduced body weight gain during lactation and after weaning in association with reduced food consumption after weaning, and a tendency towards reversibility upon dose reduction	
There were no remarkable findings for gestation length, litter size and viability, sex ratio, survival rate at 35 days postpartum and macroscopic appearance of the reproductive organs. Administration of 15000 ppm in feed for the entire duration of the study corresponded to a daily 2-mercaptobenzothiazole intake levels of approx. 1100 mg/kg body weight during gestation, 1545 to 2895 mg/kg body weight during lactation and 2000 mg/kg body weight in F1 animals aged 21 to 35 days. In the second study group, intake levels were also approx. 1100 mg/kg body weight/day during gestation and initially approx. 1725 mg/kg body weight/day during lactation but approx. 1055 mg/kg body weight/day upon reduction of the 2-mercaptobenzothiazole concentration, and the F1 animals of this group had an intake of approx. 700 mg/kg body weight/day at age 21 to 35 days. Study in accordance with the TSCA guideline (EPA, 1985 a, 1987, 1988). The 2-mercaptobenzothiazole used was 98.5 and 98.1% pure (see the above-mentioned studies conducted by Springborn Laboratories).						
Three-generation study, rat (no further details)	5000 ppm in feed	no indication of any effects on reproduction or lactation				FMC, 1957

Table 10. Reproductive toxicity of 2-mercaptobenzothiazole

Type of study, test system	Dose (mg/kg body weight/day or mg/m³)	Parental toxicity	Embryotoxicity/foeto-toxicity	Teratogenicity	Development of offspring	Reference
Dominant-lethal test, Sprague-Dawley rat, 28 males and 56 females/dose, oral administration in the males' feed from 70 days prior to and during mating with 2 untreated females per male, examination on day 13 of gestation	control (cytoxan as a positive control and basal diet as the negative control)					Rodwell et al., 1991; Springborn Laboratories, 1989 e
	ca. 95–238 (*2500 ppm in feed)	short depression of body weight gain*	no findings*	not studied	not studied	
	ca. 341–769 (*8750 ppm in feed)	reduced body weight gain and feed consumption (males)*	no findings*	not studied	not studied	
	ca. 585–1335 (*15000 ppm in feed)	reduced body weight gain and feed consumption (males)*	no findings*	not studied	not studied	

* No effect on male fertility or the number of pre- or postimplantation losses.
Study in accordance with the TSCA guideline (EPA, 1985 a, 1987). The 2-mercaptobenzothiazole used was 98.1% pure.

Table 10. Reproductive toxicity of 2-mercaptobenzothiazole

Type of study, test system	Dose (mg/kg body weight/day or mg/m³)	Parental toxicity	Embryotoxicity/foeto-toxicity	Teratogenicity	Development of offspring	Reference
Embryotoxicity study and dominant-lethal test, albino rat, 11–25 rats/group; 1st group: oral administration to females on days 1 and 3 of oestrus, mating with males which had been dosed twice with 2-mercaptobenzothiazole at an interval of 3 days (no precise details); 2nd group: oral administration to females on days 4 and 11 of gestation, mating with untreated males, sacrifice on day 19 of gestation (test substance was the commercial product Captax, purity not specified)	control (sunflower oil)					Aleksandrov, 1982
	200 (1st group)	increased length of oestrus cycle	reduced foetal weight, increased total and postimplantation embryonic mortality	not studied	not studied	
	200 (2nd group)	no information	reduced foetal weight, increased total embryonic mortality	not studied	not studied	
The investigator discussed the problem that it was impossible on the basis of the study findings to judge by what mechanism (dominant-lethal mutations or toxicity during pregnancy) embryonic mortality was increased. Inadequate conduct and documentation render the study unsuitable for evaluation of 2-mercaptobenzothiazole with respect to reproductive toxicity and mutagenicity (only one dose was tested; females mated with treated males were also given 2-mercaptobenzothiazole (making it impossible to distinguish whether the observed embryonic mortality was induced by dominant-lethal mutations or toxicity during pregnancy); no information was given on the treatment administered to males; statistical analysis was not performed and/or not documented).						

End of Table 10

Beginning of Table 11

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans					
Type of study	Induction	Challenge	Incidence of positive findings	Evaluation by the investigators	Reference
1. Tests in dermatologically healthy subjects					
Maximisation test, 25 male subjects	25% applied dermally, 48-hour occlusive exposure, 5 times, upon pretreatment with 5% sodium lauryl sulphate (24-hour occlusive exposure to induce moderate irritation)	10% applied dermally, 48-hour occlusive exposure, 48 hours after pretreatment with 10% sodium lauryl sulphate (1-hour occlusive exposure to induce subclinical irritation)	9/24	moderately sensitising	Kligman, 1966; Magnusson and Kligman, 1970
The purity of the 2-mercaptobenzothiazole used was not specified.					
Patch test, 50 subjects	50% applied dermally, 24-hour occlusive exposure, 3 times/week, 15 exposures in total	patch application after 10 to 14 days	0/50	not sensitising	Monsanto, 1987; Product Investigations, 1976
Test substance was the commercial product Thiotax, formulated in dimethyl phthalate, purity not specified.					

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
2. Studies in groups of individuals with occupational exposure to 2-mercaptobenzothiazole or rubber products				
2.1 Employees working in the rubber-manufacturing and processing industry				
Patch test	workers at a rubber-processing plant in Nokia, Finland; January 1976 to December 1980 (annual average of 1798 employees); during this period covered by the report there were 21 cases of occupational allergic contact dermatitis in which compensation was paid by the insurance company	rubber chemicals (MBT, MBT mix, MMBT)	+ 1 compensated case (positive reaction to MBT, MBT mix and MMBT)	Kilpikari, 1982
Patch test	workers at 5 shoe factories in the Emilia-Romagna region of Italy; 1992 to 1994 (246 in total, 201 females, 45 males; 16/246 (6.5%) with allergic contact dermatitis particularly of the hands and arms)	ECDRG test series (MBT: 1%, MBT mix: 2% in petrolatum)	+ 3/246 (1.2%) reacted to MBT, + 1/246 (0.4%) reacted to MBT mix	Mancuso et al., 1996
Patch test	workers at plants where, inter alia, 2-mercaptobenzothiazole was used; 1971 (1088)	rubber chemicals (MBT: 2% in petrolatum)	+ 11/1088 (1%)	Ziegler and Süß, 1974/75
Patch test	patients with positive patch test reactions to rubber chemicals; 1953 to 1958 (63, 16 of whom worked in the rubber industry)	rubber chemicals (MBT)	+ 34/63 (54%); 10/16 (62.5%) of those patients working in the rubber industry	Herrmann and Schulz, 1960
Patch test	patients with occupational exposure to leather or shoes who were treated at centres belonging to the Informationsverbund Dermatologischer Kliniken (Information Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies in Germany), January 1990 to December 1994 (61)	DKG standard test series (MBT: 2% in petrolatum)	+ 3/61 (4.9%)	Koch et al., 1996
Patch test	workers at a rubber tyre factory, 1983 to 1985 (204)	standard series (MBT mix)	– 0/204 (0%) reacted to MBT mix	Zina et al., 1987

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	workers with skin disorders employed at a plant producing decorative equipment built of paper impregnated with phenol-formaldehyde resins; December 1985 to September 1986 (89, controls: 89 patients from a dermatology department)	expanded ICDRG standard test series (MBT mix)	– 0/89 (0%) reacted to MBT mix; control: + 3/89 (3.4%) reacted to MBT mix	Bruze and Almgren, 1988
2.1.1	**Employees working in the rubber-manufacturing and processing industry, case reports**			
Patch test	a worker (52 years old) employed in polyurethane production had erythema of the hands, forearms, nape and face	chemicals used in polyurethane production	– reaction to MBT, positive reactions to the monobenzyl ether of hydroquinone, 2-mercaptobenzimidazole, 2,5-di-tert.-butylhydroquinone	Higashi and Matsumura, 1987
2.2	**Employees in the metal-working industry**			
Patch test	metalworkers with suspected allergic contact dermatitis caused by cutting oils containing 2-mercaptobenzothiazole (12)	cutting oils and cutting oil ingredients (MBT: 1% in petrolatum)	+ 7/12 (58.3%)	Fregert and Skog, 1962
Patch test	metalworkers with suspected allergic contact dermatitis (100)	standard series and rubber chemicals (MBT: 2% in petrolatum)	+ 15/100 (15%)	Conde-Salazar and Urcuyo, 1976
Patch test	metalworkers with dermatitis of the hands and/or forearms (40, 8 of them with established contact sensitisation)	ICDRG test series, chemicals encountered in the working environment (MBT: 1% in petrolatum, MBT mix: 2% in petrolatum)	+ 1/40 (2.5%) reacted to MBT mix	de Boer et al., 1989
Patch test	metalworkers with suspected allergic contact dermatitis due to cutting oils were tested at 2 centres in the United Kingdom; 1986 to 1987 (174, 157 males, 17 females, 43% with at least one positive patch test reaction)	ICDRG test series, cutting oil ingredients (MBT mix)	+ 2/174 (1.2%) reacted to MBT mix	Grattan et al., 1989
Patch test	Singapore metalworkers with dermatitis; January 1986 to December 1990 (274, 180 males, 94 females, 57 (65.7%) with at least one positive patch test reaction)	ICDRG standard test series (MBT: 1% in petrolatum)	– 0/274 (0%)	Goh and Yuen, 1994
2.3	**Employees working in photographic film production or processing**			
Patch test	employees at a film developing laboratory in Stockholm, Sweden; 1983 to 1986 (65, 13 (20%) with at least one positive patch test reaction)	film chemicals (MBT: 2% in petrolatum)	– 0/65 (0%)	Lidén, 1989
Patch test	female employee (45 years old) at a film production plant developed dermatitis of both hands upon handling film emulsions	no precise details (MBT)	+ 1/1	Rudzki et al., 1981
2.4	**Hospital staff with occupational contact with products containing 2-mercaptobenzothiazole, particularly gloves**			
Patch test	surgeons with allergic contact dermatitis of the hands due to surgical gloves (11)	NACDG test series (MBT: 0.333% CBS, MBTS and MMBT in petrolatum)	+ 7/11 (63.6%) reacted to MBT mix	Fisher, 1975, 1985
Patch test	staff member at a hospital in Perugia, Italy, with work-related allergic contact dermatitis; 1992 to 1993 (14)	GIRDCA test series (MBT: 1%)	+ 2/14 (14.3%)	Stingeni et al., 1995

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	staff at a hospital in Turku, Finland, with dermatitis of the hand; 1970 to 1979 (102)	ICDRG test series (MBT mix)	+ 3/102 (2.9%) reacted to MBT mix	Lammintausta et al., 1982 a
Patch test	health service workers at a hospital in Warsaw, Poland, with suspected occupational allergic contact dermatitis (152)	hospital's own test series (MBT)	+ 1/152 (0.7%)	Rudzki, 1979
Patch test	staff (kitchen personnel, cleaners, assistant nurses, operating theatre nurses) at a hospital in Turku, Finland, frequently doing so-called wet work (536 and 586 (the data given in the two publications differs), 115 (21.5 and 19.6%, respectively) with at least one positive patch test reaction)	expanded ICDRG test series (MBT mix)	+ 1/536 or 586 (ca. 0.2%) reacted to MBT mix	Lammintausta, 1983; Lammintausta et al., 1982 b
Patch test	staff at a hospital in Groningen, the Netherlands, with suspected allergic contact dermatitis due to rubber chemicals (12)	rubber chemicals (MBT mix: MBT, MBTS, CBS and MMBT in petrolatum, each 0.25%)	– 0/12 (0%) reacted to MBT mix	Nater, 1975
Patch test	health personnel at a hospital in Tampere, Finland (512, 23 of whom had a positive scratch test reaction to latex gloves)	ICDRG test series (MBT mix)	– 0/23 (0%) reacted to MBT mix	Turjanmaa, 1987
2.5 Occupational contact dermatitis in the working population in general				
Patch test	Swedish post office employees with contact eczema from wearing rubber bank-note counters (24); controls: post office employees without contact eczema after wearing rubber bank-note counters (20), dermatological patients hospitalised for other reasons (10)	rubber chemicals and products (MBT: 1% in petrolatum)	+ 15/24 (62.5%) – 0/30 (0%; controls)	Eriksson and Östlund, 1968
Patch test	patients with allergic contact dermatitis of the hands from work-related wearing of protective gloves (5)	rubber chemicals and glove material (MBT: 1% in petrolatum)	+ 1/5 (20%) (MBT chemically not detectable in the glove material)	Kaniwa et al., 1994 b
Patch test	miners with suspected allergic contact dermatitis of the feet from wearing rubber shoes (25), 17 of whom had positive patch test reactions to rubber chemicals	rubber chemicals, known allergens (MBT: 1% in Eucerin)	+ 11/25 (44%)	Götz and Istvanovic, 1963
Patch test	workers with occupational contact dermatitis of the feet from wearing safety shoes (13)	materials and chemicals used in the shoe industry (MBT: 1% in petrolatum)	+ 2/13 (15.4%)	Foussereau et al., 1986
Patch test	patients with occupational contact dermatitis at a hospital in England; 1968 to 1977 (292)	European standard series (MBT and MBT mix)	+ 12/292 (4.1%) reacted to MBT and/or MBT mix	Wilkinson et al., 1980
Patch test	patients with suspected occupational allergic contact dermatitis at a hospital in Lodz, Poland; January 1989 to March 1994 (334, 46 (13.8%) with at least one positive patch test reaction)	hospital's own test series (MBT: 2% in petrolatum)	+ 11/334 (3.3%) or 11/46 (23.9%) of patients, depending on reference group, had positive patch test reactions	Kiec-Swierczynska, 1995
Patch test	Danish post office employees with contact eczema from wearing rubber fingerstalls (51)	rubber chemicals and products (MBT: 2% in petrolatum)	+ 1/51 (2%)	Roed-Petersen et al., 1977
Patch test	patients with suspected occupational allergic contact dermatitis of the hands at a hospital in Brussels, Belgium; (400, 225 males, 175 females, 197 (49.3%) with at least one positive patch test reaction)	expanded ICDRG test series (MBT mix: 2% in petrolatum)	+ 7/400 (1.75%) reacted to MBT mix (1.7% of men and 1.8% of women)	Lachapelle and Tennstedt, 1979

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	Workers with suspected allergic contact dermatitis at a paper mill and a dairy in Sweden (63) and a control group consisting of workers without skin lesions (15)	standard series, materials found in the working environment (MBT: 1% in petrolatum)	+ 1/63 (1.6%) of workers with skin lesions and 0/15 in the control group	Meding et al., 1993
Patch test	cattle farm workers and milkers with dermatoses of the hands in the Netherlands (32, 15 (47%) with at least one positive patch test reaction)	rubber chemicals, known allergens (MBT mix: MBT, MBTS, CBS and MMBT in paraffin, 0.25% each; MBT: 1% in paraffin (only tested in 6 subjects))	– 0/32 (0%) reacted to MBT mix + 1/6 (17%) reacted to MBT mix	te Lintum and Nater, 1973; Nater, 1975
Patch test	hairdressers with suspected occupational allergic contact dermatitis; 1981 (24)	work-related chemicals (MBT: 2%)	– 0/24 (0%)	Warshawshki et al., 1981
Patch test	workers with inflammatory lesions of the lips after wearing gas masks at a copper-smelting plant (57)	no information	+ 22 positive to rubber chemicals (Captax, Altax, Thiurad and/or Neozon D)	Antoniev and Gerasimenko, 1976
2.5.1 Occupational contact dermatitis in the working population in general, case reports				
Patch test	worker (male, 53 years old, fitter) with pustulosis palmaris upon occupational contact with black rubber mats	ICDRG standard test series (MBT: 2% in petrolatum)	+ reaction to MBT, MMBT, thiurams and carbamates	Schoel and Frosch, 1990
Patch test	rubber tyre factory worker (37 years old) with forearm and facial eczema	European standard series, rubber chemicals and MBT mix)	+ reaction to MMBT	Azenha and Basto, 1990
Patch test	miner with allergic contact dermatitis (no further details in the English abstract of the publication written in Czech)	no precise details	+ reaction to MBT and MBTS	Hegyi, 1990
Patch test	potter (57 years old) with chronic eczema of the hand after working with an oil which contained 1% MBT	European standard series (MBT)	+ reaction to MBT and neomycin	Wilkinson et al., 1990, 1991
Patch test	female patient (58 years old) with dermatitis of the hands upon handling industrial greases	ICDRG test series and rubber chemicals (MBT)	– reaction to MBT	Kalimo et al., 1989
3. Studies in patient populations				
3.1 Studies in patients with confirmed or suspected allergic contact dermatitis from rubber chemicals				
Patch test	patients with contact eczema from wearing or handling rubber products; 1934 to 1941 (74)	rubber chemicals and products (MBT: 2% in oil)	+ 53/74 (71.6%)	Bonnevie and Marcussen, 1945
Patch test	patients with contact eczema from wearing or handling rubber products; 1955 to 1967 (102)	rubber chemicals (MBT)	+ 46/102 (45.1%)	Wilson, 1969
Patch test	patients with dermatitis of the hands from wearing rubber gloves (42)	rubber chemicals (MBT)	+ 15/42 (35.7%)	Wilson, 1960
Patch test	patients with allergic contact dermatitis from rubber products in Poland; 1962 to 1981 (335)	standard test series (MBT: 2% in petrolatum)	+ 30%	Rudzki et al., 1982
Patch test	patients with allergic eczematous contact dermatitis at a hospital; 1968 to 1970 (540 patients not specifically suspected to have been sensitised to rubber chemicals and an additional 229 patients specifically suspected to have been sensitised to rubber chemicals and/or shoes)	hospital's own test series (MBT: 1% in petrolatum)	+ 7.8% of the general cohort and 18.8% of the patients with suspected allergies to rubber and/or shoes	Baer et al., 1973

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans

Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	patients with contact dermatitis at two Belgian hospitals (810, 55 of whom had positive patch test reactions to rubber chemicals)	standard test series (MBT mix: MBT, MBTS, CBS and MMBT, each 1% in petrolatum)	+ 10/810 (1.2%) of all patients or 10/55 (18.2%) of patients reacting to rubber chemicals had positive reactions to MBT mix	Song et al., 1979
Patch test, RAST and scratch test	patients with contact urticaria caused by rubber products (7)	NACDG test series (MBT: 1% in petrolatum)	+ (1/7, patch test and scratch test), RAST test negative	Belsito, 1990
Patch test	rubber eczema patients (8)	hospital's own test series comprising rubber chemicals and known allergens (MBT and MBT derivatives: 1% in "Eucerin anhydric.")	+ 1/8 (12.5%) reacted to MBT and MBT derivatives	Bandmann, 1956
Patch test	patients with suspected allergic contact dermatitis at a Spanish hospital; 1978 to 1988 (4680 (3264 males, 1416 females), of whom 2526 had positive patch test reactions, 686 of whom, in turn, had positive reactions to rubber chemicals)	GEIDC test series, rubber chemicals (MBT mix: CBS, MBTS and MMBT, each 0.5% in petrolatum, and MBT: test concentration not specified)	+ 83/4680 (1.8%) of all patients or 83/2526 (3.3%) of patients with positive patch test reactions or 83/686 (12%) of patients with positive reactions to rubber chemicals reacted to MBT; + 111/4680 (2.4%) of all patients or 111/2526 (4.4%) of patients with positive patch test reactions or 111/686 (16.2%) of patients with positive reactions to rubber chemicals reacted to MBT mix	Conde-Salazar et al., 1993
Patch test	patients at a hospital in Erlangen-Nuremberg, Germany; January 1985 to March 1990 (3851, 1617 males and 2234 females, of whom 145 had positive patch test results to at least one rubber chemical)	hospital's own test series, patient-specific chemicals (MBT, MBT mix, MBTS, CBS and MMBT, each 0.5%)	+ 5/3851 (0.1%) of all patients or 5/145 (3.4%) of patients reacting to rubber chemicals had positive reactions to MBT; + 15/3851 (0.4%) of all patients or 15/145 (10%) of patients reacting to rubber chemicals had positive reactions to MBT mix	von Hintzenstern et al., 1991
Patch test	patients with allergic contact dermatitis caused by rubber or plastic gloves (63)	ICDRG standard test series (MBT: 2% in petrolatum)	+ 3/63 (4.8%)	Estlander et al., 1986
Patch test	patients with allergic contact dermatitis caused by rubber gloves, surgical gloves and/or vinyl gloves; 1969 to 1984 (21)	ECDRG test series, hospital's own test series comprising rubber chemicals (MBT: 2% in petrolatum)	+ 1/21 (4.7%)	Frosch et al., 1987

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	patients with contact dermatitis (369), 52 of whom had positive patch test reactions to rubber chemicals	no details (MBT)	+ 15/369 (4.1%) of all patients or 15/52 (28.8%) of patients with positive reactions to rubber chemicals	Vincze and Korossy, 1979
Patch test	patients with suspected allergic contact dermatitis caused by rubber chemicals at a hospital in Toronto, Canada; 1981 to 1988 (316 (22%) with at least one positive patch test reaction)	rubber chemicals (MBT: 1%, MBT mix: 1 and 2%)	+ 11/316 (3.5%) reacted to MBT; + 9 and 10/316 (2.8 and 3.3%) reacted to 1 and 2% MBT mix, respectively	Holness and Nethercott, 1997
Patch test	patients with suspected allergic contact dermatitis from rubber chemicals (2075)	hospital's own test series (MBT: 2% in paraffin)	+ 3.25%; 2.46% of male and 4.05% of female patients	Rudzki and Grzywa, 1975; Rudzki et al., 1976
Patch test	patients with suspected allergic contact dermatitis from rubber chemicals at a hospital in Rostock, Germany; 1991 to 1995 (135, 31 of whom had allergic and 30 had irritating contact dermatitis)	standard test series (MBT: 1%, MBT mix: 2%)	+ 2/135* (1.48%) reacted to MBT; + 2/135 reacted to MBT mix (1/135)	Heise et al., 1997
* An additional 1/135 reacted positive with regard to allergic contact dermatitis from MBT.				
Patch test	patients with suspected allergic contact dermatitis from rubber chemicals at a hospital in Dortmund, Germany; January 1990 to October 1991 (198; 98 males and 100 females)	ICDRG test series, rubber chemicals (MBT: 2% in petrolatum)	+ 6/198 (3%)	Geier et al., 1994
Patch test	patients with suspected allergic contact dermatitis from rubber chemicals at a hospital in Turku, Finland; 1980 to 1982 (3332; 995 males and 2337 females, 158 (4.7%) with at least one positive patch test reaction)	ICDRG test series, rubber chemicals (MBT mix: MBT, MBTS, CBS and MMBT, 0.5% each)	+ 19/3332 (0.6%) reacted to MBT mix, 0.8% of men and 0.5% of women)	Lammintausta and Kalimo, 1985
3.1.1 Studies in patients with confirmed or suspected allergic contact dermatitis from rubber chemicals, case reports				
Patch test	female patient (68 years old) with dermatitis of the eyelids after taking eyedrops supplied in a bottle with a rubber stopper; history of rubber-glove dermatitis	eyedrop components, standard series (MBT and MBT mix: 2% in petrolatum)	+ reaction to MBT and mercapto mix	Calnan and Cronin, 1981
Patch test	Patient (male, 56 years old, dermatologist) with an immediate reaction after wearing a diving mask	rubber chemicals (MBT: 1%)	– reaction to MBT	Tuyp and Mitchell, 1989
3.2 Studies in patients with confirmed or suspected allergic contact dermatitis in general				
Patch test	children (2 to 14 years old) with dermatoses (190, 67 of whom with positive patch tests)	GEIDC test series (MBT: 2% in petrolatum)	+ 8/67 (12%)	De la Cuadra Oyanguren et al., 1989
Patch test	patients with positive patch test reactions at a hospital in Vancouver, Canada (35)	NACDG test series (MBT and MBT mix)	+ 4/35 (11.4%) reacted to MBT; + 6/35 (17.1%) reacted to MBT mix	Mitchell, 1977
Patch test	contact dermatitis patients at a hospital (779)	MBT	49/779 (6.3%)	Bourrinet et al., 1979

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	patients at a hospital; September 1963 to September 1966 (376)	hospital's own test series (MBT: 1% in petrolatum)	+ 22/376 (5.9%)	Epstein et al., 1968
Patch test	patients at a hospital in Warsaw, Poland; September 1967 to January 1970 (1205, 50.4% with at least one positive patch test reaction)	hospital's own test series (MBT: 2% in paraffin)	+ 59/1205 (4.9%); 4.5% of male and 5.1% of female patients	Rudzki and Kleniewska, 1970
Patch test	patients from 10 North American hospitals; January 1971 to June 1972 (1200)	NACDG test series (MBT: 2%*)	+ 58/1200 (4.8%)	Rudner et al., 1973; Rudner, 1977
* Rudner (1977) states that MBT mix was tested.				
Patch test	patients with suspected allergic contact dermatitis at a hospital in Salvador, Brazil; 1976 (536)	hospital's own test series (MBT: 5%)	+ 25/536 (4.7%); 5.2% of male and 4.2% of female patients	Moriearty et al., 1978
Patch test	patients from North American hospitals; 1974 to 1975 (1900)	NACDG test series (MBT: 1%, MBT mix: 1%)	+ 4.1% reacted to MBT, + 3.3% reacted to MBT mix	Rudner, 1977
Patch test	patients with suspected allergic contact dermatitis at a hospital in Toronto, Canada (200, 47% with at least one positive patch test reaction)	standard test series (MBT: 2%, MBT mix: 1% in petrolatum)	+ 8/200 (4%) reacted to MBT, + 2/200 (1%) reacted to MBT mix	Nethercott, 1982
Patch test	patients with suspected allergic contact dermatitis at a hospital in Glasgow, Scotland; April 1970 to December 1973 (1312; 603 males, 709 females; 716 (54.6%) with a positive patch test reaction)	ICDRG test series (MBT: 1%)	+ 60/1312 (4.6%); 19/603 (3.2%) of male and 41/709 (5.8%) of female patients	Husain, 1977
Patch test	patients with suspected allergic contact dermatitis at a hospital in Taipei, Taiwan; 1978 to 1979 (76)	hospital's own test series (MBT: 1% in petrolatum)	+ 3/76 (3.9%)	Sun, 1980
Patch test	patients (children) at a hospital in Philadelphia, PA, USA; 1971 to 1976 (653, 98 (15%) with at least one positive patch test reaction)	NACDG test series (MBT)	+ 23/653 (3.5%)	Leyden and Kligman, 1979
Patch test	patients from Poland, Bulgaria, Hungary and the former GDR and CSSR who had at least one positive patch test reaction; 1979 (2231; 953 males, 1278 females)	standard test series (MBT: 2% in petrolatum)	+ 71/2231 (3.2%)	Schubert et al., 1982
Patch test	patients from 6 North American hospitals; 1977 to 1981 (2297)	no precise details (MBT: 1%, MBT mix: MBTS, CBS and MMBT, each 0.25% in petrolatum)	+ 73/2297 (3.2%) reacted to MBT and/or MBT mix	Lynde et al., 1982 a
Patch test	patients from North American hospitals; 1975 to 1976 (900 to 2000)	NACDG test series (MBT: 1%, MBT mix: 1%)	+ 3.1% reacted to MBT, + 2.4% reacted to MBT mix	Rudner, 1977
Patch test	patients from North American hospitals; July 1972 to June 1974 (3125 (Rudner (1977) gives 3000 individuals as the cohort size for the 1972–1974 period))	NACDG test series (MBT mix: 1%)	+ 3% reacted to MBT mix	Rudner et al., 1975; Rudner, 1977
Patch test	patients with suspected allergic contact dermatitis at a hospital in Brussels, Belgium; 1967 to 1968 (300; 184 males, 116 females)	ICDRG standard test series (MBT: 2% in petrolatum)	+ 9/300 (3%); 2.2% of male and 4.3% of female patients	Oleffe et al., 1972

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	patients with suspected allergic contact dermatitis from 10 North American hospitals; January 1984 to May 1985 (1132 and 1141)	expanded NACDG test series (MBT: 1% and MBT mix: 1% in petrolatum)	+ 33/1141 (2.9%) and + 30/1132 (2.7%) reacted to MBT and MBT mix, respectively	Storrs et al., 1989
Patch test	patients from 6 European and North American hospitals; 1971 to 1974 (5947)	no details (MBT: 1%, MBT mix: MBT, MBTS, CBS and MMBT, each 0.25% in petrolatum)	+ 171/5947 (2.9%) reacted to MBT and/or MBT mix	Lynde et al., 1982 a; Mitchell et al., 1976
Patch test	patients at a hospital; 1954 to 1956 (401)	rubber chemicals (MBT: 1% in petrolatum)	+ 11/401 (2.7%)	Gaul, 1957
Patch test	patients with eczema at a hospital in Vancouver, Canada; 1972 to 1981 (4190; 1492 males, 2698 females)	hospital's own test series (MBT: 1%, MBT mix: MBT, MBTS, CBS and MMBT, each 0.25%, or MBTS, CBS, MMBT, each 0.33%, in petrolatum)	+ 109/4190 (2.6%); 2.4% of male and 3.0% of female patients reacted to MBT and/or MBT mix	Lynde et al., 1982 b
Patch test	patients at a hospital in Melbourne, Australia; 1976 to 1978 (486)	standard test series (MBT: 1% in paraffin, MBT mix)	+ 12/486 (2.5%) reacted to MBT and/or MBT mix	Nurse, 1979
Patch test	patients from 8 Hungarian hospitals (2847)	hospital's own test series (MBT)	+ 71/2847 (2.5%)	Korossy, 1979
Patch test	patients with suspected allergic contact dermatitis at a hospital in Singapore; 1978 (844)	hospital's own test series (MBT: 1% in petrolatum)	+ 20/844 (2.4%)	Rajan and Khoo, 1980
Patch test	patients at a hospital in Liverpool, Great Britain (403)	ICDRG test series (MBT and MBT mix)	+ 9/403 (2.2%) reacted to MBT, + 10/403 (2.5%) reacted to MBT mix	Macfarlane et al., 1989
Patch test	patients at a hospital in Wycombe, England; 1974 to 1976 (992)	European standard series (MBT and MBT mix)	+ 22/992 (2.2%) reacted to MBT and/or MBT mix	Wilkinson et al., 1980
Patch test	patients with suspected allergic contact dermatitis at a hospital in Edinburgh, Scotland; October 1970 to May 1985 (496; 193 males and 303 females; 339 (68.3%) with at least one positive patch test reaction)	ICDRG test series (MBT: 2%, MBT mix: 2%)	+ 11/496 (2.2%) reacted to MBT, + 16/496 (3.2%) reacted to MBT mix	Vestey et al., 1986
Patch test	patients (children, mean age 9.2 years) with suspected allergic contact dermatitis at a hospital in Glasgow, Scotland; 1979 to 1993 (92)	European standard series (MBT, MBT mix)	+ 2/92 (2.2%) reacted to MBT, + 2/92 (2.2%) reacted to MBT mix	Stables et al., 1996
Patch test	patients from 14 North American hospitals; August 1985 to July 1989 (3968 and 3979); the publication by Holness et al. (1995) gives the size of the study cohort as 4055 individuals	NACDG test series (MBT: 1%, MBT mix: MBTS, CBS and MMBT, each 0.33% in petrolatum)	+ 2.1% reacted to MBT, + 2.5% reacted to MBT mix	Nethercott et al., 1991; Holness et al., 1995
Patch test	patients with atopic dermatitis at a hospital in Poland (93)	hospital's own test series (MBT: 2% in petrolatum)	+ 2/93 (2.1%)	Rudzki and Grzywa, 1975

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	dermatitis patients from 8 European hospitals; March 1967 to July 1968 (4825; 2039 males, 2786 females, 45% with at least one positive patch test reaction), by participating centres: Copenhagen, Denmark (800; 300 males, 500 females) Gothenburg, Sweden (800; 262 males, 538 females) London, UK (800; 358 males, 442 females) Lund, Sweden (800; 320 males, 480 females) Munich, Germany (800; 377 males, 423 females) Wycombe, UK (132; 53 males, 79 females) Bari, Italy (315; 202 males, 113 females) Nijmegen, the Netherlands (378; 166 males, 212 females)	ICDRG standard test series (MBT: 2% in petrolatum)	+ 98/4825 (2.0%; 1.7% males, 2.3% females) + 22/800 (2.75%) + 8/800 (1%) + 38/800 (4.75%) + 10/800 (1.25%) + 9/800 (1.13%) + 7/132 (5.3%) + 2/315 (0.6%) + 2/378 (0.5%)	Bandmann et al., 1972; Fregert et al., 1969; Gabler-Sandberger, 1975
Patch test	patients with suspected allergic contact dermatitis at a Chinese hospital; March 1988 to March 1989 (204; 69 males, 135 females; 119 with a positive patch test reaction)	European standard test series (MBT and MBT mix: test concentrations not specified)	+ 4/204 (2%) and + 6/204 (2.7%) reacted to MBT and MBT mix, respectively	Fan and Zhao, 1990
Patch test	patients from 6 Scandinavian hospitals (Bergen, Helsinki, Copenhagen, Lund, Gothenburg, Stockholm); 1964 to 1965 (1629; 756 males and 873 females; 551 (33.8%) with at least one positive patch test reaction)	test series comprising 10 chemicals (MBT: 2% in petrolatum)	+ 2% (probably 15/756) of male patients and 1% (probably 9/873) of female patients	Magnusson et al., 1966
Patch test	patients (children) with suspected allergic contact dermatitis in Aalborg, Denmark; 1975 to 1980 (168, 77 (45.8%) of whom had at least one positive patch test reaction)	ICDRG test series (MBT mix)	+ 3/168 (1.8%) reacted to MBT mix	Veien et al., 1982
Patch test	patients with suspected allergic contact dermatitis from 2 Hungarian hospitals; October 1965 to July 1968 (1284)	hospital's own test series (MBT: 2% in petrolatum)	+ 22/1284 (1.7%)	Korossy et al., 1969
Patch test	patients with suspected allergic contact dermatitis at a hospital in Saskatoon, Canada; January 1983 to June 1987 (468)	standard test series (MBT mix)	+ 1.6% (1.8% of male patients and 1.5% of female patients) reacted to MBT mix	Hogan et al., 1988
Patch test	patients from 8 hospitals in western Slovakia (5266; 1675 males, 3591 females)	hospital's own test series (MBT: 2% in petrolatum)	+ 81/5266 (1.54%; 1.61% of male patients and 1.5% of female patients)	Hegyi et al., 1994
Patch test	patients at a hospital in Manchester, Great Britain (4721 or 4722 (equivocal data))	ICDRG test series (MBT mix)	+ 73/4722 (1.5%) or 77/4721 (1.6%) (equivocal data) reacted to MBT mix	Shehade et al., 1991
Patch test	patients at a hospital in Lagos, Nigeria; 1979 to 1983 (453)	standard test series (MBT mix)	+ 7/453 (1.5%) reacted to MBT mix	Olumide, 1985
Patch test	hospital patients; 1985 to 1988 (1244, 45% of whom had positive patch test results)	ICDRG test series (MBT mix)	+ 16/1244 (1.3%) reacted to MBT mix	Caperan et al., 1990

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	patients with suspected allergic contact dermatitis from 6 Danish hospitals; September 1985 to February 1986 (2166; 696 males, 1470 females)	European standard test series (MBT mix: 2% in petrolatum)	+ 26/2166 (1.2%); 10/696 (1.4%) of male patients and 16/1470 (1.1%) of female patients reacted to MBT mix	Christophersen et al., 1989
Patch test	patients with suspected allergic contact dermatitis at a hospital in Nagoya, Japan; 1976 to 1979 (256)	ICDRG test series (MBT mix: 2%)	+ 3/256 (1.2%) reacted to MBT mix	Hirano and Yoshikawa, 1982
Patch test	patients with suspected allergic contact dermatitis at a hospital in Utrecht, the Netherlands; 1974 (250)	known allergens (MBT mix: 1%)	+ 3/250 (1.2%) reacted to MBT mix	Young and Houwing, 1987
Patch test	patients with suspected allergic contact dermatitis at a hospital in Utrecht, the Netherlands; 1984 (614)	known allergens (MBT mix: 1%)	+ 7/614 (1.1%) reacted to MBT mix	Young and Houwing, 1987
Patch test	patients at a hospital in Munich, Germany; 1971 to 1972 (3067; 1339 males, 1728 females)	probably the ICDRG test series	+ 1.1% of male patients and 0.9% of female patients	Gabler-Sandberger, 1975
Patch test	patients (children) with suspected allergic contact dermatitis at a hospital in Strasbourg, France; 1969 to 1978 (87)	ICDRG test series (MBT)	+ 1/87 (1.1%)	Levy et al., 1980
Patch test	patients with suspected allergic contact dermatitis at 12 Italian hospitals; January 1984 to December 1988 (23541, 60% of whom had at least one positive patch test reaction)	GIRDCA test series (MBT: 1%, MBT mix)	incidences by test year as % of positive patch test results + 0.8–1.1% (MBT), + 0.9–1.1% (MBT mix)	Gola et al., 1992
Patch test	patients at a hospital in Prague, former CSSR; 1982 to 1984 (807; 372 (46%) with at least one positive patch test reaction)	hospital's own test series (MBT: 2% in petrolatum)	+ 8/807 (1%)	Machácková, 1986
Patch test	patients at centres belonging to the Informationsverbund Dermatologischer Kliniken (Information Network of Departments of Dermatology for the surveillance and scientific evaluation of contact allergies in Germany); January 1990 to December 1994 (20067)	DKG standard test series	+ 180/20067 (0.9%)	Koch et al., 1996
Patch test	patients with suspected allergic contact dermatitis at a hospital in Toronto, Canada; 1981 to 1988 (1353)	ECDRG or NACDG test series (MBT: 1%, MBT mix: 1 and 2%)	+ 12/1353 (0.9%) reacted to MBT; + 12 and 19/1353 (0.9 and 1.4%) reacted to MBT mix (1 and 2%, respectively)	Holness and Nethercott, 1997
Patch test	patients at a hospital in Odense, Denmark; 1973 to 1977 (3225; 1451 males, 1774 females; 1038 (38%) with at least one positive patch test reaction)	ICDRG test series (MBT mix)	+ 30/3225 (0.9%) of all patients or 30/1038 (2.9%) of patients with a positive patch test reacted to MBT mix	Hammershoy, 1980
Patch test	contact dermatitis patients from Italian hospitals; 1984 to 1987 (18497)	GIRDCA test series (MBT: 1%, MBT mix)	+ 146/18497 (0.8%) and + 178/16783 (1%) reacted to MBT and MBT mix, respectively	Sertoli et al., 1989
Patch test	eczema and dermatitis patients at a hospital in Beijing, China, 1989 (124)	European standard series (MBT mix: 2%)	+ 1/124 (0.8%) reacted to MBT mix	Zhang et al., 1991

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	individuals with suspected allergic contact dermatitis of the hands in a group of 20000 randomly selected inhabitants (20 to 65 years old) of Gothenburg, Sweden (1081; 355 males, 726 females)	standard test series (MBT mix: 2%)	+ 0.7% reacted to MBT mix (1.1% of men and 0.6% of women)	Meding and Swanbeck, 1990
Patch test	patients with suspected allergic contact dermatitis of the hands, in particular; October 1968 to January 1969 (140; 71 males and 69 females; 49 (35%) with at least one positive patch test reaction)	hospital's own test series (MBT: 1% in petrolatum)	+ 1/140 (0.7%)	Agrup et al., 1970
Patch test	patients at a hospital in Munich, Germany; 1977 to 1983 (12026; 4775 males, 7202 females, 49 of unspecified sex; 4494 (37.4%) with at least one positive patch test reaction (Gollhausen et al. (1988) give the size of the cohort as 11962))	standard test series (MBT mix: MBT, CBS, MBTS and MMBT, each 0.25% in petrolatum)	+ 68/12026 (0.6%; 0.7% of men and 0.5% of women) reacted to MBT mix	Enders et al., 1988;Gollhausen et al., 1988
Patch test	patients at a hospital in Hamburg, Germany; January 1976 to December 1980 (5348; 2071 males, 3277 females; 1320 (24.7%) with at least one positive patch test reaction)	ICDRG standard test series (MBT: 1% in petrolatum)	+ 34/5348 (0.6%)*	Kuhlwein and Hausen, 1982
* The publication gives an incidence of 1.4% for the 34 out of 5348 patients with a positive reaction to MBT, which seems implausible.				
Patch test	patients with suspected allergic contact dermatitis at a hospital in Nagoya, Japan; 1976 1977, 1979, 1980 (178)	NACDRG test series (MBT: 1%, MBT mix: 1%)	+ 1/178 (0.6%) reacted to MBT, – 0/178 (0%) reacted to MBT mix	Hirano and Yoshikawa, 1982
Patch test	patients from 8 German hospitals; 1990 to 1991 (4160; 40% males, 60% females; 47% with at least one positive patch test reaction)	DKG test series (MBT)	+ 0.5% (0.7% of men and 0.4% of women)	Schnuch et al., 1993
Patch test	patients of 21 dermatologists practising in Northern Germany; 1987 to 1989 (5766)	expanded ECDRG test series (MBT mix: 2% in petrolatum)	+ 18/5766 (0.3%) reacted to MBT mix	Scheuer et al., 1992
Patch test	patients at a Swedish hospital; 1969 to 1979 (8933)	ICDRG test series (MBT mix: test concentration not specified)	+ 0.3% (incidence of positive patch test reactions to MBT mix expected for 1980 on the basis of the analysis of the 1969–1979 data; actually found: 1.1%)	Edman and Möller, 1982
Patch test	patients at a hospital in Prague, former CSSR; 1979 to 1984 (888; 380 (42.3%) with at least one positive patch test reaction)	hospital's own test series (MBT: 2% in petrolatum)	+ 2/888 (0.2%)	Novák and Kvicalová, 1985
Patch test	patients with suspected allergic contact dermatitis at a hospital in Marseilles, France (500)	standard test series and patient-specific chemicals (MBT: 2% in petrolatum)	+ 1/500 (0.2%)	Calas et al., 1978
Patch test	children with atopic dermatitis; 1970 to 1975 (270; 0 to 12 years old; 154 boys, 116 girls; 25 children with positive patch tests)	hospital's own test series (MBT mix: 2% in petrolatum)	– 0/270 (0%) reacted to MBT and MBT mix	Angelini and Meneghini, 1977

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Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
3.3	**Studies in patients with confirmed or suspected allergic contact dermatitis caused by shoes**			
Patch test	patients with allergic contact dermatitis of the feet which according to patch-testing was attributable to shoe chemicals or materials; results from 8 European and American hospitals; 1953 to 1981, by participating hospitals:	chemicals and materials used in the shoe industry	% patients with positive reactions to shoe chemicals or materials	Lynde et al., 1982 c
	Vancouver, Canada; 1977 to 1981 (119; 32 with positive patch test reactions)	(MBT: 2% in petrolatum)	+ 9/32 (28.1%)	
	Bari, Italy; 1974 to 1979 (165; 108 with positive patch test reactions)	(MBT: 1% in petrolatum)	+ 5/108 (4.8%)	
	Richmond, VA, USA; 1972 (25)	(MBT)	+ 9/25 (36%)	
	San Francisco, CA, USA; 1969 (43)	(MBT: 1% in petrolatum)	+ 5/43 (11.6%)	
	Athens, Greece; 1974 (25)	(MBT: 1% in petrolatum)	+ 6/25 (24%)	
	London, UK; 1953 to 1959 (102)	(MBT: 1% in petrolatum)	+ 27/102 (26.4%)	
	London, UK; 1966 to 1959 (213)	(MBT: 1% in petrolatum)	+ 82/213 (38.4%)	
Patch test	patients (children) with suspected allergic contact dermatitis of the feet at a hospital in Bordeaux, France; January 1990 to September 1995 (8)	ECDRG test series (MBT mix: 2% in petrolatum)	+ 5/8 (62.5%) reacted to MBT, + 4/8 (50%) reacted to MBT mix	Roul et al., 1996
Patch test	patients with contact dermatitis of the feet; 1982 to 1983 (6)	ICDRG test series (MBT)	+ 3/6 (50%)	Zaitz et al., 1987
Patch test	patients with contact dermatitis of the feet; 1968 to 1971 (35)	chemicals used in the shoe industry (MBT: 2% in petrolatum)	+ 15/35 (42.9%)	Adams, 1972
Patch test	patients with suspected allergic contact dermatitis of the feet (24, 12 of whom had positive patch tests)	chemicals used in the shoe industry (MBT and MBT mix: test concentrations not specified)	+ 5/12 (41.7%) reacted to MBT, + 7/12 (58.3%) reacted to MBT mix	Freeman, 1983
Patch test	patients with suspected allergic contact dermatitis of the feet (25, 21 of whom had positive patch tests)	chemicals used in the shoe industry (MBT)	+ 9/25 (36%)	Jordan, 1972
Patch test	patients with suspected allergic contact dermatitis of the feet (59, 42 of whom had positive patch tests)	chemicals used in the shoe industry (MBT: 1% in petrolatum)	+ 13/42 (30.9%)	Dahl, 1975
Patch test	patients at a hospital in Sydney, Australia, with allergic contact dermatitis of the feet which upon patch-testing was attributable to shoe chemicals or materials; 1987 to 1997 (55)	ECDRG test series (MBT and MBT mix: 2%)	+ 20/55 (36%) reacted to MBT, + 22/55 (40%) reacted to MBT mix	Freeman, 1997
Patch test	patients with dermatitis, especially of the feet, upon contact with rubber products, particularly shoes (30)	MBT and MBT derivatives (CBS, MBTS, MMBT), rubber chemicals (MBT and MBT derivatives: each 1% in petrolatum)	+ 9/30 (30%) reacted to MBT, in most cases also to the MBT derivatives*	Kaniwa et al., 1987, 1990 a, b, 1992, 1994 a; Kantoh et al., 1984

* Chemical analysis demonstrated the presence of the compounds in shoe material, and skin sensitisation was shown in the guinea pig maximisation test (only carried out for a few patients and samples).

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans

Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	patients with contact dermatitis of the feet (24)	chemicals used in the rubber industry (MBT and MBT derivatives: 1% in petrolatum)	+ 6/24 (25%) reacted to MBT, + 8/24 (33.3%) reacted to MBT derivatives	Blank and Miller, 1952
Patch test	female patients with contact dermatitis of the feet (25)	chemicals used in the shoe industry (MBT: 1% in petrolatum)	6/25 (24%)	Varelzides et al., 1974
Patch test	patients with allergic eczema of the feet; 1961 (9)	rubber chemicals and chemicals used in the shoe industry	+ 2/9 (22%) reacted to benzothiazole compounds	de Vries, 1964
Patch test	patients in Lisbon, Portugal, with contact dermatitis of the feet; 1974 to 1985 (539)	hospital's own test series consisting of 12 chemicals, and the European standard test series (MBT: 2% in petrolatum and MBT mix: test concentrations not specified)	+ 109/539 (20.2%) reacted to mercapto mix	Correia and Brandao, 1986
Patch test	patients with contact dermatitis of the feet; 1962 to 1966 (17)	chemicals used in the shoe industry (benzothiazole compounds: 1%)	+ 3/17 (17.6%)	Suurmond and Verspijck Mijnssen, 1967
Patch test	children with suspected allergic contact dermatitis of the feet (34)	NACDG test series (MBT and MBT mix: 1%)	+ 4/34 (11.8%) reacted to MBT and MBT mix	Weston et al., 1983
Patch test	patients with contact dermatitis of the feet due to wearing rubber boots; April 1992 to June 1995 (9)	rubber chemicals (MBT: 1% in petrolatum)	+ 1/9 (11.1%)	Nishioka et al., 1996
Patch test	patients with suspected allergic contact dermatitis from rubber products (31; probably some of the patients also belonged to the cohort studied by Kaniwa (see above))	rubber chemicals (MBT: 1%)	+ 3/31 (9.7%)	Kantoh et al., 1985
Patch test	patients with suspected allergic contact dermatitis of the feet (74, 43 of whom had positive patch tests)	chemicals used in the shoe industry (MBT: 1% in petrolatum)	+ 4/43 (9.3%)	Epstein, 1969
Patch test	patients with contact dermatitis of the feet (19)	chemicals used in the shoe industry (MBT: 1% in paraffin)	+ 1/19 (5.3%)	Ross and Obst, 1969
Patch test	patients with eczematous contact dermatitis of the feet; 1975 to 1980 (165; 98 males, 67 females; 108 (65.4%) with at least one positive patch test reaction)	chemicals used in the shoe industry and known contact allergens (MBT: 1% in petrolatum)	+ 8/165 (4.8%)	Angelini et al., 1980
Patch test	patients with dermatitis of the feet (103, 46 (44.7%) with at least one positive patch test reaction)	test series consisting of known contact allergens and chemicals used in the shoe industry (MBT)	+ (incidence not given)	Liu et al., 1993
3.3.1 Studies in patients with confirmed or suspected allergic contact dermatitis caused by shoes, case reports				
Patch test	patient (male, 46 years old) with foot dermatitis	no information	+ reaction to MBT	Rietschel, 1984
Patch test	female patient (49 years old) with dermatitis on the soles of her feet	ICDRG test series (MBT and MBT mix)	+ reaction to MBT, MBT mix, CBS and MMBT	Pecegueiro and Brandao, 1984
Patch test	girl (8 years old) with dermatitis of the lips after inflating a rubber balloon, and foot dermatitis after wearing tennis shoes	no information	+ reaction to MBT, thiuram and a perfume mix	Rudzki and Rebandel, 1995

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	boy (13 years old) with foot dermatitis	GEIDC test series (MBT and MBT mix)	+ reaction to MBT and MBT mix	Romaguera et al., 1989
Patch test	boy (8 years old) with foot dermatitis after wearing tennis shoes	shoe materials and chemicals used in the shoe industry, extracts prepared from the shoes (MBT, MBTS)	+ reaction to MBT and MBTS*	Jung, 1991; Jung et al., 1988
* The compounds were detected in the shoe material by chemical analysis.				
3.4	**Studies in patients with confirmed or suspected allergic contact dermatitis caused by garments containing spandex (a polyurethane elastomer fibre; spandex materials sold commercially under the brand names, Lycra, Vyrene, Numa and Blue "C", contained no 2-mercaptobenzothiazole (Fisher 1967 a, b; Lockey, 1974))**			
Patch test	female patients with contact dermatitis after wearing brassieres containing spandex; 1966 (11)	fabric and chemicals (MBT: 1% in petrolatum)	+ 11/11 (100%)	Allenby et al., 1966
Patch test	female patients with contact dermatitis after wearing brassieres made of fabrics containing polyurethane (spandex, Lycra; 5)	fabric and chemicals (MBT: 1% in petrolatum)	+ 5/5 (100%)	Porter and Sommer, 1967
Patch test	female patients with contact dermatitis after wearing brassieres made of fabrics containing polyurethane (spandex, Wonderlastic; 3)	standard series and rubber chemicals (MBT: 2% in petrolatum)	+ 2/3 (66%)	van Dijk, 1968
Patch test	female patients with contact dermatitis after wearing brassieres or girdles made of fabrics containing polyurethane (spandex; 10)	fabric and chemicals (MBT: 1% in petrolatum)	+ 6/10 (60%)	Joseph and Maibach, 1967
Patch test	female patients with contact dermatitis after wearing brassieres or girdles made of fabrics containing polyurethane (spandex, Lycra; 9)	fabric and chemicals, known allergens (MBT: 1% in petrolatum)	– 0/9 (0%)	Carr, 1967
3.4.1	**Studies in patients with confirmed or suspected allergic contact dermatitis caused by garments containing spandex (a polyurethane elastomer fibre; spandex materials sold commercially under the brand names, Lycra, Vyrene, Numa and Blue "C", contained no 2-mercaptobenzothiazole (Fisher 1967 a, b)), case reports**			
Patch test	female patient (44 years old) with contact dermatitis after wearing a brassiere made of polyurethane-containing fabric (spandex)	fabric and rubber chemicals	+ 1/1	Munro-Ashman, 1966
Patch test	female patient (27 years old) with contact dermatitis after wearing a brassiere made of polyurethane-containing fabric (spandex)	fabric and MBT (1%)	+ 1/1	Tanenbaum, 1967
3.5	**Studies in patients with confirmed or suspected allergic contact dermatitis caused by medical prostheses**			
Patch test	spinal injury patients who developed signs of allergic contact dermatitis of the penis after wearing rubber condom urinals (50)	rubber chemicals of the ICDRG test series, condom material (MBT mix)	+ 11/50 (22%) reacted to MBT mix	Bransbury, 1979
Patch test	patients with dermatitis caused by wearing lower limb prostheses (6) or orthopaedic corsets (2)	GIRDCA standard series and chemicals used in the plastics industry	+ 1/8 (12.5%) reacted to MBT and MBT mix	Balato et al., 1995
3.5.1	**Studies in patients with confirmed or suspected allergic contact dermatitis caused by medical prostheses, case reports**			
Patch test	patient (male, 77 years old) with dermatitis due to Foley catheters (Silastic® Foley catheter, Dow Corning Corp. Medical Products; indwelling catheter following resection of the penis)	ICDRG test series (MBT and MMBT: 1%, MBT mix: 0.5% in petrolatum)	+ reaction to MBT, MBT mix and MMBT	Ancona et al., 1985

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans				
Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
Patch test	patient (male, 39 years old) with contact dermatitis caused by wearing a suction socket lower-limb prosthesis	GEIDC test series (MBT and MBT derivatives: 1% in petrolatum, MBT mix: 2% in petrolatum)	+ reaction to MBT, MBT derivatives and MBT mix	Conde-Salazar et al., 1989
Patch test	male patient with foot dermatitis and dermatitis caused by wearing a leg prosthesis	GEIDC test series (MBT mix)	+ reaction to MBT mix	Correcher and Perez, 1981
3.6 Studies in patients with immediate-type reactions, particularly to latex products				
Patch test, prick test	patients with dermatitis caused by rubber gloves (7, 4 of whom showed immediate-type reactions (urticaria))	rubber chemicals, latex (MBT: 1%)	– 0/7 (4/7 had positive reactions to latex in the prick test)	Köpman and Hannuksela, 1983
Patch test	patients with anaphylactic reactions to rubber gloves made of natural latex (5)	rubber chemicals, natural latex	+ 1/5 reacted to MBT mix, another female patient had a positive patch test to rubber chemicals, immediate-type reactions to natural latex	Kleinhans, 1984 a, b; Galinsky and Kleinhans, 1982
Patch test, RAST test	patients with anaphylactic reactions to rubber gloves made of latex (3)	rubber chemicals, latex (MBT: 1%)	– 0/3 reacted to MBT, positive patch test with immediate-type reactions to latex, positive RAST test with latex, elevated latex-specific IgE	Seifert et al., 1987
3.6.1 Studies in patients with immediate-type reactions, particularly to latex products, case reports				
Patch test, RAST	operating theatre nurse (female, 34 years old) with anaphylactic reactions to rubber gloves made of latex (3)	rubber chemicals, latex	– reaction to MBT and other rubber chemicals, positive patch test with immediate-type reactions to natural latex, positive RAST with natural latex, elevated latex-specific IgE	Spaner et al., 1989
Patch test	operating theatre nurse (female, 25 years old) with anaphylactic reactions to rubber gloves made of latex (3)	no information	+ reaction to MBT, latex-specific IgE (RAST class 3.1)	Groß, 1990
Patch test	patient with a Foley catheter (male, 71 years old) had anaphylactic reactions to the catheter and a history of allergic contact dermatitis due to rubber chemicals (thiurams, carbamates, MBT)	no information	+ reaction to MBT, thiurams and carbamates; latex-specific IgE (RAST class 3)	Guimaraens et al., 1992
No test	patients with anaphylactic reactions following intravenous administration of contrast agents, one case involving a disposable syringe with latex rubber components and the other an ampoule with a latex rubber seal (2)	no tests were carried out; the author suspected that the MBT detected in the latex rubber products in question was the cause of the anaphylactic reactions		Hamilton, 1987, 1990

Table 11. Sensitising potential of 2-mercaptobenzothiazole in humans

Type of study	Group (n)	Test series (for MBT: test concentrations and vehicle, where specified)	Positive findings (incidence)[a)]	Reference
3.7 Patients with photoallergic reactions to 2-mercaptobenzothiazole				
Patch test	patient (male, 54 years old; the English abstract of the publication written in Japanese provides no further details)	rubber chemicals (MBT, wavelength of light: 350 nm)	+ patch test reaction intensified by light irradiation	Hara et al., 1981

a) Incidences are given only for positive reactions to MBT and MBT mix; positive reactions to other chemicals studied in the various test series are not listed.

MBT 2-mercaptobenzothiazole

MBT mix mixture of various MBT derivatives, as a rule N-cyclohexyl-2-benzothiazylsulphenamide (CBS), dibenzothiazyl disulphide (MBTS) and morpholinyl mercaptobenzothiazole (MMBT), and in some cases also 2-mercaptobenzothiazole

ECDRG European Contact Dermatitis Research Group

DKG Deutsche Kontaktallergie Gruppe

ICDRG International Contact Dermatitis Research Group

NACDG North American Contact Dermatitis Group

RAST radioallergosorbent test for quantitative determination of antigen-specific IgE levels in serum

GEIDC Spanish Group for Research of Contact Dermatitis

GIRDCA Gruppo Italiano Ricerca Dermatiti da Contatto e Ambientali

End of Table 11

References

Adams, R.M.
Shoe dermatitis
Calif. Med., 117, 12–16 (1972)

Agrup, G., Dahlquist, I., Fregert, S., Rorsman, H.
Value of history and testing in suspected contact dermatitis
Arch. Dermatol., 101, 212–215 (1970)

Aleksandrov, S.E.
Effect of vulcanization accelerators on embryonic mortality in rats
Bull. Exp. Biol. Med., 93, 107–109 (1982)

Allenby, C.F., Crow, K.D., Kirton, V., Munro-Ashman, D.
Contact dermatitis from spandex yarn
Br. Med. J., 1, 674 (1966)

Ancona, A., de la Torre, R.S., Evia, J.R.
Dermatitis from mercaptobenzothiazole in a Foley catheter
Contact Dermatitis, 13, 339–340 (1985)

Anderson, B.E., Zeiger, E., Shelby, M.D., Resnick, M.A., Gulati, D.K., Ivett, J.L., Loveday, K.S.
Chromosome aberration and sister chromatid exchange test results with 42 chemicals
Environ. Mol. Mutagen., 16, Suppl. 18, 55–137 (1990)

Angelini, G., Meneghini, C.L.
Contact and bacterial allergy in children with atopic dermatitis
Contact Dermatitis, 3, 163–174 (1977)

Angelini, G., Vena, G.A., Meneghini, C.L.
Shoe contact dermatitis
Contact Dermatitis, 6, 279–283 (1980)

Antoniev, A.A., Gerasimenko, I.V.
On occupational contact cheilites
Vestn. Dermatol. Venerol., 1, 56–60 (1976)
See also: Chem. Abstr., 85, 129775r (1976)

Arthur D. Little, Inc.
Results of corneal, dermal and acute toxicity studies involving polaroid samples #476, #477, #478 and #479 (1977)
On behalf of the Polaroid Corporation
NTIS/OTS 0520673

Axelsson, J.G.K., Johansson, S.G.O., Wrangsjö, K.
IgE-mediated anaphylactoid reactions to rubber
Allergy, 42, 46–50 (1987)

Azenha, A., Basto, A.S.
Airborne contact dermatitis from rubber
Contact Dermatitis, 23, 250 (1990)

Baer, R.L., Ramsey, D.L., Biondi, E.
The most common contact allergens
Arch. Dermatol., 108, 74–78 (1973)

Bakke, J.E., Feil, V.J., Zaylskie, R.G.
Isotope dilution assay for urinary methanesulfinic and methanesulfonic acids: application to detection of methylthio turnover
Biomed. Environ. Mass Spectrom., 18, 1096–1098 (1989)

Balato, N., Costa, L., Lembo, G., Patruno, C., Cuccurullo, F.M., Parascandolo, F., Scognamiglio, D., Ayala, F.
Allergic contact dermatitis from orthopaedic devices
Contact Dermatitis, 32, 314–315 (1995)

Bandmann, H.J.
Vulkanisationsbeschleuniger als Kontaktekzemallergene (Zur Analyse des „Gummiekzems“)
Hautarzt, 7, 419–421 (1956)

Bandmann, H.J., Calnan, C.D., Cronin, E., Fregert, S., Hjorth, N., Magnusson, B., Maibach, H., Malten, K.E., Meneghini, C.L., Pirilä, V., Wilkinson, D.S.
Dermatitis from applied medicaments
Arch. Dermatol., 106, 335–337 (1972)

Bannister, R.M., Beyrouty, P., Robinson, K., Broxup, B., Barnett, J.W., Jr.
Acute and subchronic neurotoxicity evaluation of 2-mercaptobenzothiazole (MBT) in rats
Toxicologist, 11, 117 (1991)

Barlogova, S., Stolcova, E.
The observation of allergogenic effect of 2-mercaptobenzothiazole and 2-mercaptobenzoimidazole
Prac. Lék., 36, 13–16 (1984)

Basketter, D.A., Scholes, E.W.
Comparison of the local lymph node assay with the guinea-pig maximization test for the detection of a range of contact allergens
Food Chem. Toxicol., 30, 65–69 (1992)

Basketter, D.A., Selbie, E., Scholes, E.W., Lees, D., Kimber, I., Botham, P.A.
Results with OECD recommended positive control sensitizers in the maximization, Buehler and local lymph node assays
Food Chem. Toxicol., 31, 63–67 (1993)

Basketter, D.A., Scholes, E.W., Kimber, I.
The performance of the local lymph node assay with chemicals identified as contact allergens in the human maximization test
Food Chem. Toxicol., 32, 543–547 (1994)

Bayer AG
Product data sheet Vulkacit Merkapto (1995 a)

Bayer AG
Product data sheet Vulkacit Merkapto/C (1995 b)

Bayer AG
Product data sheet Vulkacit Merkapto/MG (1995 c)

Bayer AG
Product data sheet Vulkacit Merkapto/MGC (1995 d)

Belsito, D.V.
Contact urticaria caused by rubber
Dermatol. Clin., 8, 61–66 (1990)

BFG (BF Goodrich Company)
Bioassay: Ames Salmonella/microsome, laboratory identification number: 22, compound name: 2-mercaptobenzothiazol
Unpublished report (1984)

Bionetics Research Laboratories, Inc.
Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals, Volume I. carcinogenic study
Report, Contracts PH 43-64-57 and PH 43-67-735 (1968 a)
On behalf of the National Cancer Institute, USA
NTIS/PB-223 159

Bionetics Research Laboratories, Inc.
Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals, Volume II. teratogenic study in mice and rats
Report, Contracts PH 43-64-57 and PH 43-67-735 (1968 b)
On behalf of the National Cancer Institute, USA
NTIS/PB-223 160

Bio-Research Laboratories Ltd.
A range-finding acute study of potential effects of 2-mercaptobenzothiazole on locomotor activity in rats
Unpublished report, Project No. 83800 (1989 a)
On behalf of the Chemical Manufacturers Association

Bio-Research Laboratories Ltd.
An acute study of the potential neurotoxic effects of 2-mercaptobenzothiazole in rats
Unpublished report, Project No. 83801 (1989 b)
On behalf of the Chemical Manufacturers Association

Bio-Research Laboratories Ltd.
A 3-month study of the potential effects of orally administered 2-mercaptobenzothiazole on behavior and neuromorphology in rats
Unpublished report, Project No. 83568 (1990)
On behalf of the Chemical Manufacturers Association

Blank, I.H., Miller, O.G.
A study of rubber adhesives in shoes as the cause of dermatitis of the feet
JAMA, 149, 1371–1374 (1952)

de Boer, E.M., van Ketel, W.G., Bruynzeel, D.P.
Dermatoses in metal workers (II). Allergic contact dermatitis
Contact Dermatitis, 20, 280–286 (1989)

Bonnevie, P., Marcussen, P.V.
Rubber products as a widespread cause of eczema. Report of 80 cases
Acta Derm. Venereol., 25, 163–178 (1945)

Bourrinet, P., Puchault, P., Sarrazin, G., Berkovic, A.
Etude comparée de quelques substances allergéniques chez l'homme et chez le cobaye
J. Pharm. Belg., 34, 21–26 (1979)

Bransbury, A.J.
Allergy to rubber condom urinals and medical adhesives in male spinal injury patients
Contact Dermatitis, 5, 317–323 (1979)

Brewster, D.W., Mirly, K.J., Wilson, A.G.E., Barnett, J.W., Jr.
Lack of in vivo DNA binding of mercaptobenzothiazole to selected tissues of the rat
Biochem. Biophys. Res. Commun., 165, 342–348 (1989 a)

Brewster, D.W., Mirly, K.J., Wilson, A.G., Barnett, J.W.
Lack of in vivo DNA binding of mercaptobenzothiazole (MBT) to selected tissues of the rat
Toxicologist, 9, 128 (1989 b)

Bruze, M., Almgren, G.
Occupational dermatoses in workers exposed to resins based on phenol and formaldehyde
Contact Dermatitis, 19, 272–277 (1988)

BUA (Beratergremium für umweltrelevante Altstoffe der Gesellschaft Deutscher Chemiker)
2-Mercaptobenzothiazol
BUA-Stoffbericht 74 (June 1991)
VCH Verlagsgesellschaft mbH, Weinheim (1992)

Calas, E., Castelain, P.Y., Piriou, A.
Épidémiologie des dermatoses de contact à Marseille
Ann. Dermatol. Venereol., 105, 345–347 (1978)

Calnan, C.D., Cronin, E.
False positive reaction to mercaptobenzthiazole from rubber in eyedrop bottle
Contact Dermatitis, 7, 283–284 (1981)

Cannon Laboratories, Inc.
Skin sensitization study of CR-141 and ? in guinea pigs
Report No. 7E-6314 (1977)
On behalf of Hercules, Incorporated
NTIS/OTS 0200534

Caperan, D., Reymond, J.L., Zambelli, P., Beani, J.C., Amblard, P.
Les tests cutanés dans l'allergie de contact. Tendance évolutive sur les quatre dernières années
Nouv. Dermatol., 9, 853–854 (1990)

Carr, R.D.
Spandex dermatitis
Arch. Dermatol., 96, 642–645 (1967)

Carrillo, T., Cuevas, M., Munoz, T., Hinojosa, M., Moneo, I.
Contact urticaria and rhinitis from latex surgical gloves
Contact Dermatitis, 15, 69–72 (1986)

Christophersen, J., Menné, T., Tanghøj, P., Andersen, K.E., Brandrup, F., Kaaber, K., Osmundsen, P.E., Thestrup-Pedersen, K., Veien, N.K.
Clinical patch test data evaluated by multivariate analysis
Contact Dermatitis, 21, 291–299 (1989)

CIVO TNO (Central Institute for Nutrition and Food Research)
Determination of the acute oral toxicity of five samples of mercaptobenzthiazole in rats
Unpublished report (1977)
On behalf of WTR

Collins, J.J., Strauss, M.E., Riordan, S.G.
Mortalities of workers at the Nitro plant with exposure to 2-mercaptobenzothiazole
Occup. Environ. Med., 56, 667–671 (1999)

Colucci, D.F., Buyske, D.A.
The biotransformation of a sulfonamide to a mercaptan and to mercapturic acid and glucuronide conjugates
Biochem. Pharmacol., 14, 457–466 (1965)

Conde-Salazar, L., Urcuyo, J.F.G.
Sensibilidad a los componentes de la goma en obreros de la construccion
Actas Dermo-Sifilograficas, 67, 297–310 (1976)

Conde-Salazar, L., LLinas Volpe, M.G., Guimaraens, D., Romero, L.
Allergic contact dermatitis from a suction socket prosthesis
Contact Dermatitis, 19, 305–306 (1989)

Conde-Salazar, L., del-Rio, E., Guimaraens, D., González Domingo, A.
Type IV allergy to rubber additives: a 10-year study of 686 cases
J. Am. Acad. Dermatol., 29, 176–180 (1993)

Corning Hazleton
Hexyl cinnamic aldehyde, 2-mercaptobenzothiazole, eugenol, propyl paraben, m-aminophenol, dimethyl isophthalate, isoeugenol and trimellitic anhydride: local lymph node assay in the mouse
Unpublished report No. 0000/188-1032 (1996)

Correcher, B.L., Perez, A.G.
Dermatitis from shoes and an amputation prosthesis due to mercaptobenzthiazole and paratertiary butyl formaldehyde resin
Contact Dermatitis, 7, 275 (1981)

Correia, S., Brandao, F.M.
Contact dermatitis of the feet
Dermatosen, 34, 102–106 (1986)

Crebelli, R., Falcone, E., Aquilina, G., Carere, A.
In vitro mutagenicity of rubber chemicals and their nitrosation products
Toxicol. Lett., 23, 307–313 (1984 a)

Crebelli, R., Falcone, E., Aquilina, G., Carere, A., Paoletti, A., Fabri, G.
Mutagenicity studies in a tyre plant: in-vitro activity of urine concentrates and rubber chemicals
IARC Sci. Publ., 59, 289–295 (1984 b)

Crebelli, R., Paoletti, A., Falcone, E., Aquilina, G., Fabri, G., Carere, A.
Mutagenicity studies in a tyre plant: in vitro activity of workers' urinary concentrates and raw materials
Br. J. Ind. Med., 42, 481–487 (1985)

De la Cuadra Oyanguren, J., Marquina Vila, A., Martorell Aragones, A., Sanz Ortega, J., Aliaga Boniche, A.
Dermatitis alérgica de contacto en la infancia: 1972–1987
An. Exp. Pediatr., 30, 363–366 (1989)

Dahl, M.V.
Allergic contact dermatitis from footwear. Shoe dermatitis in 42 patients
Minn. Med., 58, 871–874 (1975)

Datsenko, I.I., Korneychuk, E.P.
Kinetik des Austausches von 2-Mercaptobenzthiazol im Organismus von Tieren (German translation of the Russian)
Gig. Sanit., issue 1, 51–53 (1991)

Datsenko, I.I., Korneychuk, E.P.
Toxicokinetics of 2-mercaptobenzthiazol
Curr. Toxicol., 1, 161–166 (1993)

DFG (Deutsche Forschungsgemeinschaft, Kommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe)
List of MAK and BAT Values 2000
Wiley-VCH Verlag GmbH, Weinheim (2000)

Dieke, S.H., Allen, G.S., Richter, C.P.
The acute toxicity of thioureas and related compounds to wild and domestic Norway rats
J. Pharmacol. Exp. Ther., 90, 260–270 (1947)

van Dijk, E.
Contact dermatitis due to spandex
Acta Derm. Venereol., 48, 589–591 (1968)

Donner, M., Husgafvel-Pursiainen, K., Jenssen, D., Rannug, A.
Mutagenicity of rubber additives and curing fumes
Scand. J. Work Environ. Health, 9, 27–37 (1983)

Dow Chemical Company
Results of range finding toxicological tests on 2-mercaptobenzothiazole (Captax)
Report (1961)
NTIS/OTS 0206727

Du Pont de Nemours & Company Inc.
Toxicity of lorol-2-thiazolinyl sulfide (L-2TS) and 2-mercaptobenzothiazole (2-MT)
Report No. 10-48 (1948)
Cited in: Syracuse Research Corporation (1985)

Eastman Kodak Company, Laboratory of Industrial Medicine
Toxicity report
Report (1956)
NTIS/OTS 0206742

Eastman Kodak Company
Basic toxicity of 2-benzothiozolethiol
Report No. 114481C (1979)
NTIS/OTS 0206742

Eastman Kodak Company
Toxicity and health hazard summary
Report, Acc. No. 902638, Lab. No. 79-55, A86-10,13, A82-1, A79-37 (1980)
NTIS/OTS 0206742

Eastman Kodak Company
Environmental safety data sheet 2-benzothiazolethiol (1981)
NTIS/OTS 0206742

Ebringer, L., Lahitová, N., Foltinová, P.
Studium der Genotoxizität pharmazeutischer Präparate mittels Schnellmethode
Bratisl. Lek. Listy, 84, 645–652 (1985)

EC (European Commission)
European Chemicals Bureau, Joint Research Centre, Ispra, Italy
IUCLID data set Benzothiazole-2-thiol
CD-ROM, ed. I (1996 a)

EC (European Communities)
Official Journal of the European Communities, 39, No. L 248/206 – 248/212 (1996 b)

Edman, B.
Computerized analysis of concomitant contact allergens
Contact Dermatitis, 24, 110–113 (1991)

Edman, B., Möller, H.
Trends and forecasts for standard allergens in a 12-year patch test material
Contact Dermatitis, 8, 95–104 (1982)

Ehl, W., Hartjen, A., Thiel, C., Aulepp, H., Fuchs, E.
Latex-Allergien als IgE-vermittelte Sofortreaktionen
Allergologie, 11, 182–187 (1988)

El Dareer, S.M., Kalin, J.R., Tillery, K.F., Hill, D.L., Barnett, J.W., Jr.
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, 65–84 (1989)

Emmett, E.A., Risby, T.H., Taylor, J., Chen, C.L., Jiang, L., Feinman, S.E.
Skin elicitation threshold of ethylbutyl thiourea and mercaptobenzothiazole with relative leaching from sensitizing products
Contact Dermatitis, 30, 85–90 (1994)

Enders, F., Przybilla, B., Ring, J., Burg, G., Braun-Falco, O.
Epikutantestung mit einer Standardreihe. Ergebnisse bei 12026 Patienten
Hautarzt, 39, 779–786 (1988)

EPA (U.S. Environmental Protection Agency)
Final test guideline 40 CFR Part 798.4700
Fed. Reg. 50, No. 188, p. 39432 ff., September, 27, 1985 a

EPA (U.S. Environmental Protection Agency)
Proposed test rule 2-mercaptobenzothiazol
Fed. Reg. 50, p. 46121–46133, November 6, 1985 b

EPA (U.S. Environmental Protection Agency)
Test guideline amendments
Fed. Reg. 52, No. 97, p. 19077 ff., May, 20, 1987

EPA (U.S. Environmental Protection Agency)
EPA final test rule
Fed. Reg. 53, No. 173, p. 34514–34531, September, 7, 1988

Epstein, E.
Shoe contact dermatitis
JAMA, 209, 1487–1492 (1969)

Epstein, E., Rees, W.J., Maibach, H.I.
Recent experience with routine patch test screening
Arch. Dermatol., 98, 18–22 (1968)

Eriksson, G., Östlund, E.
Rubber bank note counters as the cause of eczema among employees at the Swedish post giro office
Acta Derm. Venereol., 48, 212–214 (1968)

Estlander, T., Jolanki, R., Kanerva, L.
Dermatitis and urticaria from rubber and plastic gloves
Contact Dermatitis, 14, 20–25 (1986)

Fan, W.X., Zhao, B.
Study on Chinese common allergens of contact dermatitis
Dermatosen, 38, 158–161 (1990)

Farr, C.H., Kirwin, C.J.
Organic sulfur compounds
In: Clayton, G.D., Clayton, F.E. (eds.)
Patty’s industrial hygiene and toxicology
4th ed., vol. II, part F, p. 4311–4372
John Wiley Sons, New York (1994)

Feinman, S.E.
Sensitivity to rubber chemicals
J. Toxicol. Cut. Ocular Toxicol., 6, 117–153 (1987)

Fisher, A.A.
Allergenic elements in spandex garments
JAMA, 201, 894 (1967 a)

Fisher, A.A.
Allergic contact spandex dermatitis
Arch. Dermatol., 96, 607–608 (1967 b)

Fisher, A.A.
“Hypoallergenic” surgical gloves and gloves for special situations
Cutis, 15, 797–811 (1975)

Fisher, A.A.
Management of dermatitis due to surgical gloves
J. Dermatol. Surg. Oncol., 11, 628–631 (1985)

FMC (Food Machinery and Chemical Corporation) (1957)
Cited in: Lehman, A.J.
Summaries of pesticide toxicity
Assoc. Food and Drug Officials of the U.S., Topeka, KS, p. 90–91 (1965)
Cited in: Syracuse Research Corporation (1985)

Foussereau, J., Cavelier, C.
La N-isopropyl-N’-phénylparaphénylènediamine a-t-elle sa place dans la batterie standard d’allergènes? Importance de cet allergène dans l’intolérance au caoutchouc
Dermatologica, 155, 164–167 (1977)

Foussereau, J., Menezes-Brandao, F., Cavelier, C., Herve-Bazin, B.
Allergy to MBT and its derivatives
Contact Dermatitis, 9, 514–516 (1983)

Foussereau, J., Muslmani, M., Cavelier, C., Herve-Bazin, B.
Contact allergy to safety shoes
Contact Dermatitis, 14, 233–236 (1986)

Freeman, S.
Shoe dermatitis
Austr. J. Dermatol., 24, 63–68 (1983)

Freeman, S.
Shoe dermatitis
Contact Dermatitis, 36, 247–251 (1997)

Fregert, S.
Cross-sensitivity pattern of 2-mercaptobenzothiazole (MBT)
Acta Derm. Venereol., 49, 45–48 (1969)

Fregert, S., Skog, E.
Allergic contact dermatitis from mercaptobenzothiazole in cutting oil
Acta Derm. Venereol., 42, 235–238 (1962)

Fregert, S., Hjorth, N., Magnusson, B., Bandmann, H.J., Calnan, C.D., Cronin, E., Malten, K., Meneghini, C.L., Pirilä, V., Wilkinson, D.S.
Epidemiology of contact dermatitis
Transactions of the St. John's Hospital Dermatological Society, 55, 17–35 (1969)

Frosch, P.J., Wahl, R., Bahmer, F.A., Maasch, H.J.
Contact urticaria to rubber cloves is IgE-mediated
Contact Dermatitis, 14, 241–245 (1986)

Frosch, P.J., Born, C.M., Schütz, R.
Kontaktallergien auf Gummi-, Operations- und Vinylhandschuhe
Hautarzt, 38, 210–217 (1987)

Fukuoka, M., Tanaka, A.
The metabolic origin of the sulfur atom in the sulfhydryl group of 2-thiobenzothiazole metabolites derived from benzothiazyl sulfenamide in the rat
Arch. Toxicol., 61, 158–160 (1987)

Fukuoka, M., Satoh, M., Tanaka, A.
Metabolism of 2-thiobenzothiazoles in the rat. Urinary, fecal and biliary metabolites of 2-benzothiazyl sulfenamides
Arch. Toxicol., 70, 1–9 (1995)

Gabler-Sandberger, E.
Das Kontaktekzem: eine Crux der Dermatologen. Undeklarierte Inhaltsstoffe verschiedener Kosmetika erschweren die Diagnose erheblich
Aerztl. Praxis, 27, 1796–1798 (1975)

Galinsky, T., Kleinhans, D.
Kontakt-Urtikaria durch Gummihandschuhe
Dermatosen, 30, 118–120 (1982)

Gaul, L.E.
Results of patch testing with rubber antioxidants and accelerators
J. Invest. Dermatol., 29, 105–110 (1957)

Geier, J., Pilz, B., Frosch, P.J., Schnuch, A.
Contact allergy due to 2-mercaptobenzimidazole
Dermatosen, 42, 190–193 (1994)

Gladyshev, V.V., Litvinchuk, M.D., Kozlenko, V.V.
Bindung von Mebethisol an Serumproteine (German translation of the Russian)
Farmatsija, 37, 48–49 (1988)

Gladyshev, V.V., Pecherskij, P.P., Golovkin, V.A., Fedotov, V.P., Kechin, I.L.
Entwicklung und Untersuchung von Vaginaltabletten mit Mebethisol auf Basis von festen Dispersionen (German translation of the Russian)
Khimiko-farmatsevticheskij Zhurnal, 25, 54–57 (1991)

Götz, H., Istvanovic, N.
Die Bedeutung von Gummiallergenen insbesondere bei Bergleuten (zur Differentialdiagnose der Tinea pedis)
Hautarzt, 14, 345–348 (1963)

Goh, C.L., Yuen, R.
A study of occupational skin disease in the metal industry (1986–1990)
Ann. Acad. Med. Singapore, 23, 639–644 (1994)

Gola, M., Sertoli, A., Angelini, G., Ayala, F., Deledda, S., Goitre, M., Lisi, P., Meneghini, C.L., Pigatto, P., Rafanelli, A., Santucci, B., Schena, D., Valsecchi, R., Zavaroni, C.
GIRDCA data bank for occupational and environmental contact dermatitis (1984 to 1988)
Am. J. Contact Dermatitis, 3, 179–188 (1992)

Gollhausen, R., Enders, F., Przybilla, B., Burg, G., Ring, J.
Trends in allergic contact sensitization
Contact Dermatitis, 18, 147–154 (1988)

Golovkin, V.A., Gladyshev, V.V., Litvinchuk, M.D.
Entwicklung und biopharmazeutische Untersuchung von Mebethisol enthaltenden Suppositorien (German translation of the Russian)
Farmatsija, 38, 10–13 (1989)

Goodwin, B.F.J., Crevel, R.W.R., Johnson, A.W.
A comparison of three guinea-pig sensitization procedures for the detection of 19 reported human contact sensitizers
Contact Dermatitis, 7, 248–258 (1981)

Goodyear (The Goodyear Tire & Rubber Company)
Mutagenicity evaluation of Captax
Unpublished report No. 79-74 (1980)

Grattan, C.E.H., English, J.S.C., Foulds, I.S., Rycroft, R.J.G.
Cutting fluid dermatitis
Contact Dermatitis, 20, 372–376 (1989)

Greim, H. (ed.)
Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründungen von MAK-Werten (Maximale Arbeitsplatzkonzentrationen)
Wiley-VCH Verlag GmbH, Weinheim (2000)

Groß, U.
Anaphylaktische Reaktion auf Gummihandschuhe bei einer Krankenschwester
Münch. Med. Wochenschr., 132, 203–204 (1990)

Guess, W.L., O'Leary, R.K.
Toxicity of a rubber accelerator
Toxicol. Appl. Pharmacol., 14, 221–231 (1969)

Guimaraens, D., Gonzalez, M.A., Condé-Salazar, L.
Occupational allergic contact dermatitis and anaphylaxis from rubber latex
Contact Dermatitis, 26, 268 (1992)

Hamilton, G.
Contamination of contrast agent by MBT in rubber seals
Can. Med. Assoc. J., 136, 1020–1021 (1987)

Hamilton, G.
Medical rubber anaphylaxis
Lancet, 336, 1453–1454 (1990)

Hammershoy, O.
Standard patch test results in 3,225 consecutive Danish patients from 1973 to 1977
Contact Dermatitis, 6, 263–268 (1980)

Hara, N., Yamada, K., Imamura, T., Hara, Y., Nishioka, K.
A case of allergic contact dermatitis associated with photocontact dermatitis, both due to MBT
Skin Res., 23, 506–512 (1981)

Hardin, B.D., Bond, G.P., Sikov, M.R., Andrew, F.D., Beliles, R.P., Niemeier, R.W.
Testing of selected workplace chemicals for teratogenic potential
Scand. J. Work Environ. Health, 7, 66–75 (1981)
See also: NTIS/OTS 0204918, NTIS/OTS 0381-0105

Hasegawa, R., Nakaji, Y., Kurokawa, Y., Tobe, M.
Acute toxicity tests on 113 environmental chemicals
Sci. Rep. Res. Inst. Tohoku Univ., -C, 36, 10–11 (1989)

Haseman, J.K., Eustis, S.L., Arnold, J.
Tumor incidences in Fischer 344 rats: NTP historical data
In: Pathology of the Fischer rat, p. 555–564
Academic Press (1990)

Hedenstedt, A., Ramel, C., Wachtmeister, C.A.
Mutagenicity of rubber vulcanization gases in Salmonella typhimurium
J. Toxicol. Environ. Health, 8, 805–814 (1981)

Hegyi, E.
Hypersensitivity to Pneumax DM (2,2‘-dibenzothiazyl disulfide) as a cause of occupational contact eczema in a miner with a group hypersensitivity to 2-mercaptobenzothiazole
Prac. Lek., 42, 436–437 (1990)

Hegyi, E., Dolezalová, A., Danilla, T., Manovská, L., Gejdos, M., Danyszová, J., Nováková, V., Cimová, V.
Inzidenz von Kontaktallergien in der West-Slowakei
Dermatosen, 42, 148–152 (1994)

Heinrich-Hirsch, B.
Possible contribution of in vitro methods to risk assessment; discussion of the presentation
In: Neubert et al. (1992), p. 471

Heise, H., Mattheus, A., Schubert, H.
Vergleichende Testung verschiedener Gummichemikalien
Dermatosen, 45, 226–228 (1997)

Herrmann, W.P., Schulz, K.H.
Hilfsstoffe der Gummiindustrie als Ekzemnoxen
Dermatologica, 120, 127–138 (1960)

Higashi, N., Matsumura, T.
A case of occupational contact dermatitis from peroxide curing agents for rubber
Skin Res., 29, 563–567 (1987)

Hintzenstern, von, J., Heese, A., Koch, H.U., Peters, K.P., Hornstein, O.P.
Frequency, spectrum and occupational relevance of type IV allergies to rubber chemicals
Contact Dermatitis, 24, 244–252 (1991)

Hirano, S., Yoshikawa, K.
Patch testing with European and American standard allergens in Japanese patients
Contact Dermatitis, 8, 48–50 (1982)

Hogan, D.J., Hill, M., Lane, P.R.
Results of routine patch testing of 542 patients in Saskatoon, Canada
Contact Dermatitis, 19, 120–124 (1988)

Holness, D.L., Nethercott, J.R.
Results of patch testing with a special series of rubber allergens
Contact Dermatitis, 36, 207–211 (1997)

Holness, D.L., Nethercott, J.R., Adams, R.M., Belsito, D., Deleo, V., Emmett, E.A., Fowler, J., Fisher, A.A., Larsen, W.G., Maibach, H.I., Marks, J., Reitschel, R.L., Rosenthal, L.E., Schorr, W.F., Storrs, F.J., Taylor, J.S.
Concomitant positive patch test results with standard screening tray in North America 1985–1989
Contact Dermatitis, 32, 289–292 (1995)

Husain, S.L.
Contact dermatitis in the west of Scotland
Contact Dermatitis, 3, 327–332 (1977)

Ikarashi, Y., Tsuchiya, T., Nakamura, A.
Evaluation of contact sensitivity of rubber chemicals using the murine local lymph node assay
Contact Dermatitis, 28, 77–80 (1993 a)

Ikarashi, Y., Tsuchiya, T., Nakamura, A.
A sensitive mouse lymph node assay with two application phases for detection of contact allergens
Arch. Toxicol., 67, 629–636 (1993 b)

Industrial Bio-Test Laboratories, Inc.
Range-finding acute oral toxicity study with intermediate 2-mercaptobenzothiazole dry batch 48/6/1001/0 in female albino rats
Report, IBT No. 8530-10076 (1977 a)
On behalf of Ciba-Geigy Corporation
NTIS/OTS 0206754

Industrial Bio-Test Laboratories, Inc.
Acute heated dust inhalation toxicity study with the intermediate 2-mercaptobenzothiazole dry in albino rats
Report, IBT No. 8562-10075 (1977 b)
On behalf of Ciba-Geigy Corporation
NTIS/OTS 0206754

Industrial Bio-Test Laboratories, Inc.
Range-finding acute dermal toxicity study with intermediate 2-mercaptobenzothiazole dry, batch 48/6/1001/0 in male albino rabbits
Report, IBT No. 8530-10076 (1977 c)
On behalf of Ciba-Geigy Corporation
NTIS/OTS 0206754

Industrial Bio-Test Laboratories, Inc.
Range-finding eye irritation test with 2-mercaptobenzothiazole dry in albino rabbits
Report, IBT No. 8530-10076 (1977 d)
On behalf of Ciba-Geigy Corporation
NTIS/OTS 0206754

Innes, J.R.M., Ulland, B.M., Valerio, M.G., Petrucelli, L., Fishbein, L., Hart, E.R., Palotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I., Peters, J.
Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note
J. Natl. Cancer Inst., 42, 1101–1114 (1969)

Istamov, K.I., Batyrbekov, A.A., Ibragimova, E.R.
Einfluß der Bestandteile der in der Latexindustrie verwendeten Ausgangsstoffe auf die Proliferation und die Differenzierung der blutbildenden Stammzellen (German translation of the Russian)
Dokl. Akad. Nauk UzSSR, 60, 59–60 (1990 a)

Istamov, K.I., Ibragimova, E.R., Batyrbekov, A.A.
Einfluß der Bestandteile des in der Latexindustrie verwendeten Ausgangsmaterials auf die Funktionsaktivität der Suppressor-T-Zellen (German translation of the Russian)
Dokl. Akad. Nauk UzSSR, 60, 52–53 (1990 b)

JETOC Newsletter
No. 4 (1985)

Johnson, G.A., Boukma, S.J., Platz, P.A.
2-Mercaptobenzothiazole, an inhibitor of dopamine β-hydroxylase
J. Pharm. Pharmacol., 22, 710–712 (1970)

Jordan, W.P.
Clothing and shoe dermatitis – recognition and management
Postgrad. Med., 52, 143–148 (1972)

Joseph, H.L., Maibach, H.I.
Contact dermatitis from spandex brassieres
JAMA, 201, 880–882 (1967)

Jung, J.H.
I. Isolation, via activity-directed fractionation, of mercaptobenzothiazole and dibenzothiazyl disulfide as two allergens responsible for shoe dermatitis. II. Bioactive constituents of Melodorum fruticosum Lour
Environ. Sci., 52, 142-B (1991)

Jung, J.H., McLaughlin, J.L., Stannard, J., Guin, J.D.
Isolation, via activity-directed fractionation, of mercaptobenzothiazole and dibenzothiazyl disulfide as 2 allergens responsible for tennis shoe dermatitis
Contact Dermatitis, 19, 254–259 (1988)

Kalimo, K., Jolanki, R., Estlander, T., Kanerva, L.
Contact allergy to antioxidants in industrial greases
Contact Dermatitis, 20, 151–152 (1989)

Kammüller, M.E., Thomas, C., De Bakker, J.M., Bloksma, N., Seinen, W.
The popliteal lymph node assay in mice to screen for the immune disregulating potential of chemicals – a preliminary study
Int. J. Immunopharmacol., 11, 293–300 (1989)

Kaniwa, M., Ikarashi, Y., Kojima, S., Nakamura, A., Kantoh, H., Itoh, M., Ishihara, M.
Chemical approach to contact dermatitis caused by household products. IV. Analysis of mercaptobenzothiazole-type accelerators in commercial rubber products and incidence of positive reactions in patch testing
Eisei Kagaku, 33, 140–148 (1987)

Kaniwa, M., Ikarashi, Y., Kojima, S., Nakamura, A., Momma, J., Nakaji, Y., Kurokawa, Y., Kantoh, H., Itoh, M.
Contact dermatitis form rubber boots: investigation of causative chemicals
Skin Res., 32, 234–242 (1990 a)

Kaniwa, M., Momma, J., Ikarashi, Y., Kojima, S., Nakamura, A., Nakaji, Y., Kurokawa, Y., Kantoh, H., Itoh, M.
Allergic contact dermatitis from rubber boots: investigation of causative chemicals by combination of patch tests (in patient and animal models) and chemical analysis
Contact Dermatitis, 23, 250 (1990 b)

Kaniwa, M., Momma, J., Ikarashi, Y., Kojima, S., Nakamura, A., Nakaji, Y., Kurokawa, Y., Kantoh, H., Itoh, M.
A method for identifying causative chemicals of allergic contact dermatitis using a combination of chemical analysis and patch testing in patients and animal groups: application to a case of rubber boot dermatitis
Contact Dermatitis, 27, 166–173 (1992)

Kaniwa, M., Isama, K., Nakamura, A., Kantoh, H., Itoh, M., Miyoshi, K., Saito, S., Shono, M.
Identification of causative chemicals of allergic contact dermatitis using a combination of patch testing in patients and chemical analysis
Contact Dermatitis, 30, 26–34 (1994 a)

Kaniwa, M., Isama, K., Nakamura, A., Kantoh, H., Hosono, K., Itoh, M., Shibata, K., Usuda, T., Asahi, K., Osada, T., Matsunaga, K., Ueda, H.
Identification of causative chemicals of allergic contact dermatitis using a combination of patch testing in patients and chemical analysis – application to cases from rubber gloves
Contact Dermatitis, 31, 65–71 (1994 b)

Kantoh, H., Hosono, K., Itoh, M., Ishihara, M., Nakamura, A., Kojima, S., Kaniwa, M.
Two cases of shoe dermatitis
Skin Res., 26, 664–671 (1984)

Kantoh, H., Ishihara, M., Itoh, M., Hosono, K., Nishimura, M.
Allergens in rubber products
HIFV, 27, 501–509 (1985)

Kayser, D., Schlede, E. (ed.)
Chemikalien und Kontaktallergie – eine bewertende Zusammenstellung
BgVV (Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin) (1995)

Kiec-Swierczynska, M.
Occupational sensitivity to rubber
Contact Dermatitis, 32, 171–190 (1995)

Kilpikari, I.
Occupational contact dermatitis among rubber workers
Contact Dermatitis, 8, 359–362 (1982)

Klaschka, F., Voßmann, D.
Kontaktallergene – Chemische, klinische und experimentelle Daten (Allergen-Liste)
Schadstoffe und Umwelt, vol. 11
Erich Schmidt Verlag (1995)

Kleinhans, D.
Soforttyp-Allergie gegen Latex: Kontakt-Urtikaria und Ekzem
Akt. Dermatol., 10, 227–228 (1984 a)

Kleinhans, D.
Contact urticaria to rubber gloves
Contact Dermatitis, 10, 124–125 (1984 b)

Kligman, A.M.
The identification of contact allergens by human assay. III. The maximization test: a procedure for screening and rating contact sensitizers
J. Invest. Dermatol., 47, 393–409 (1966)

Kloog, Y., Zatz, M., Rivnay, B., Dudley, P.A., Markey, S.P.
Nonpolar lipid methylation-identification of nonpolar methylated products synthesized by rat basophilic leukemia cells, retina and parotid
Biochem. Pharmacol., 31, 753–759 (1982)

Koch, P., Nickolaus, G., Geier, J.
Kontaktallergien bei Lederherstellern, Lederverarbeitern und in der Schuhindustrie. Fünf-Jahres-Analyse auf der Grundlage von Daten des Informationsverbundes Dermatologischer Kliniken
Dermatosen, 44, 257–262 (1996)

Köpman, A., Hannuksela, M.
Contact urticaria to rubber
Duodecim, 99, 221–224 (1983)

Korhonen, A., Hemminki, K., Vainio, H.
Embryotoxicity of benzothiazoles, benzenesulfohydrazide, and dithiodimorpholine to the chicken embryo
Arch. Environ. Contam. Toxicol., 11, 753–759 (1982)

Korhonen, A., Hemminki, K., Vainio, H.
Toxicity of rubber chemicals towards three-day chicken embryos
Scand. J. Work Environ. Health, 9, 115–119 (1983)

Korossy, S.,
Zur Epidemiologie der allergischen Kontaktdermatitis in Ungarn
Dermatosen, 27, 119–120 (1979)

Korossy, S., Vincze, E., Doroszlay, J., Munkácsi, A.
Zur Revision des Allergenspektrums der in Ungarn gebräuchlichen diagnostischen Standard-Reihe für Epikutantestung
Berufsdermatosen, 17, 252–263 (1969)

Koryakovskij, V.A., Fedotov, V.P., Yutskovskij, A.D., Gladyshev, V.V.
Klinische Untersuchung und Laboratoriumsuntersuchung der therapeutischen Wirksamkeit von innerlich angewendetem Mebethisol bei der experimentellen Mikrosporie (German translation of the Russian)
Vestn. Dermatol. Venerol., 9, 16–19 (1992)

Kowalski, Z., Bassendowska, E.
Introductory studies on the toxic action of certain accelerators of vulcanization (“D”, “M”, “DM”, “DFT”, “P-extra-N”)
Medycyna Pracy, 16, 35–43 (1965)

Kuhlwein, A., Hausen, B.M.
Standardepikutantestung: Statistische Auswertung aus fünf Jahren
Z. Hautkr., 57, 1179–1186 (1982)

Lachapelle, J.M., Tennstedt, D.
Epidemiological survey of occupational contact dermatitis of the hands in Belgium
Contact Dermatitis, 5, 244–248 (1979)

Lammintausta, K.
Hand dermatitis in different hospital workers, who perform wet work
Dermatosen, 31, 14–19 (1983)

Lammintausta, K., Kalimo, K.
Sensitivity to rubber. Study with rubber mixes and individual rubber chemicals
Dermatosen, 33, 204–208 (1985)

Lammintausta, K., Kalimo, K., Aantaa, S.
Course of hand dermatitis in hospital workers
Contact Dermatitis, 8, 327–332 (1982 a)

Lammintausta, K., Kalimo, K., Havu, V.K.
Occurrence of contact allergy and hand eczemas in hospital wet work
Contact Dermatitis, 8, 84–90 (1982 b)

Levy, A., Hanau, D., Foussereau, J.
Contact dermatitis in children
Contact Dermatitis, 6, 260–262 (1980)

Leyden, J.J., Kligman, A.M.
Contact dermatitis to neomycin sulfate
JAMA, 242, 1276–1278 (1979)

Lide, D.R., Frederikse, H.P.R. (eds.)
CRC Handbook of chemistry and physics
77th ed., p. 3-80
CRC Press, Boca Raton, New York, London, Tokyo (1996)

Lidén, C.
Occupational dermatoses at a film laboratory – follow-up after modernization
Contact Dermatitis, 20, 191–200 (1989)

te Lintum, J.C.A., Nater, J.P.
Contact-dermatitis caused by rubber chemicals in dairy workers
Berufsdermatosen, 21, 16–22 (1973)

Litton Bionetics, Inc.
Mutagenicity evaluation of BIO-76-177 CP1975 Thiotax
Report, LBI Project No. 2683 (1976)
On behalf of Monsanto Company
NTIS/OTS 0206761

Litton Bionetics, Inc.
Mutagenicity evaluation of Thiotax BO-78-240 in the mouse lymphoma forward mutation assay
Report, LBI Project No. 20989 (1979)
On behalf of Monsanto Company
NTIS/OTS 0206761

Litton Bionetics, Inc.
Evaluation of MBT in the in vitro transformation of BALB/3T3 cells assay
Unpublished report, LBI Project No. 20992 (1982)
On behalf of the Goodyear Tire & Rubber Co.

Litton Bionetics, Inc.
Mutagenicity evaluation of mercaptobenzothiazole in the mouse lymphoma forward mutation assay
Report, LBI Project No. 20989 (1985)
On behalf of the Chemical Manufacturers Association, Inc.
NTIS/OTS 0000308 and NTIS/OTS 0510918

Litvinchuk, M.D.
Bestimmung der biologischen Wirkungen des zur Stabilisierung von Vulkanisationsprozessen verwendeten 2-Mercaptobenzothiazols (German translation of the Russian)
Farmakol. Toksikol., 26, 484–488 (1963)

Litvinchuk, M.D., Likhoded, V.A., Pozdnyakova, V.T., Zaremba, E.F., Plichuk, V.G., Krotovich, N.I.
Bestimmung von Mebethisol auf seinen Wegen zur Ausscheidung aus dem Organismus (German translation of the Russian)
Vrach. Delo, 3, 31–33 (1977)

Liu, A.Y., Taylor, J.S., Berg, R., Evey, P.
Allergens causing shoe dermatitis
J. Allergy Clin. Immunol., 91, 248 (1993)

Lockey, S.D.
Dermatitis due to mercaptobenzothiazol, otherwise known as MBT
J. Asthma Res., 12, 77 (1974)

Lynde, C.W., Mitchell, J.C., Adams, R.M., Maibach, H.I., Schorr, W.J., Storrs, F.J., Taylor, J.
Patch testing with mercaptobenzothiazole and mercapto-mixes
Contact Dermatitis, 8, 273–274 (1982 a)

Lynde, C.W., Warshawski, L., Mitchell, J.C.
Screening patch tests in 4190 eczema patients 1972–81
Contact Dermatitis, 8, 417–421 (1982 b)

Lynde, C.W., Warshawski, L., Mitchell, J.C.
Patch test results with a shoewear screening tray 119 patients, 1977–80
Contact Dermatitis, 8, 423–425 (1982 c)

Macfarlane, A.W., Curley, R.K., Graham, R.M., Lewis-Jones, M.S., King, C.M.
Delayed patch test reactions at days 7 and 9
Contact Dermatitis, 20, 127–132 (1989)

Machácková, J.
Contact allergens in the years 1982 – 1984. Analysis of the results of allergologic out-patient department of the Ist dermatological clinic in Prague
Cs. Derm., 61, 9–13 (1986)

Magnusson, B., Kligman, A.M.
The identification of contact allergens by animal assay. The guinea pig maximization test
J. Invest. Dermatol., 52, 268–276 (1969)

Magnusson, B., Kligman, A.M.
Allergic contact dermatitis in the guinea pig. Identifications of contact allergens, chapter 8, p. 102–133
Charles C. Thomas Publisher, Springfield (1970)

Magnusson, B., Blohm, S.G., Fregert, S., Hjorth, N., Høvding, G., Pirilä, V., Skog, E.
Routine patch testing III – Frequency of contact allergy at six Scandinavian clinics
Acta Derm. Venereol., 46, 396–400 (1966)

Mancuso, G., Reggiani, M., Berdondini, R.M.
Occupational dermatitis in shoemakers
Contact Dermatitis, 34, 17–22 (1996)

Mårs, U., Larsson, B.S.
New thioureas and related substances intended for melanoma targeting
Pigment Cell Res., 8, 194–201 (1995)

Matthews, E.J., Spalding, J.W., Tennant, R.W.
Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in Salmonella and carcinogenicity in rodent bioassays
Environ. Health Perspect., 101, Suppl. 2, 347–482 (1993)

Maurer, T., Thomann, P., Weirich, E.G., Hess, R.
Predictive evaluation in animals of the contact allergenic potential of medically important substances. II. Comparison of different methods of cutaneous sensitization with „weak“ allergens
Contact Dermatitis, 5, 1–10 (1979)

Meding, B., Swanbeck, G.
Occupational hand eczema in an industrial city
Contact Dermatitis, 22, 13–23 (1990)

Meding, B., Torén, K., Karlberg, A.T., Hagberg, S., Wass, K.
Evaluation of skin symptoms among workers at a Swedish paper mill
Am. J. Ind. Med., 23, 721–728 (1993)

Mercieca, M.D., Rodwell, D.E., Hinderer, R.K., Murphy, S.J.
Mercaptobenzothiazole (MBT): a two-generation study using Sprague-Dawley rats
Toxicologist, 11, 112 (1991)

Mitchell, J.C.
Multiple concomitant positive patch test reactions
Contact Dermatitis, 3, 315–320 (1977)

Mitchell, J.C., Clendenning, W.E., Cronin, E., Fregert, S., Kanof, N.B., Maibach, H.J.
Patch testing with mercaptobenzothiazole and mercapto-mix
Contact Dermatitis, 2, 123–124 (1976)

Monsanto Company
Material safety data Thiotax® accelerator (1987)
NTIS/OTS 0206761

Monsanto Company
Investigation of the in vivo DNA binding of mercaptobenzothiazole to selected tissues of the rat
Unpublished report, Project No. ML-88-06 (1989)

Monsanto
Initial submission: 2-mercaptobenzothiazole: mortality study of workers employed at a European rubber chemical plant
Report (1992)
NTIS/OTS 0539232

Monsanto Company
Unpublished report No. ML-88-0426 (not dated)
Cited in: EC (1996 a)

Moriearty, P.L., Pereira, C., Guimaraes, N.A.
Contact dermatitis in Salvador, Brazil
Contact Dermatitis, 4, 185–189 (1978)

Morita, S., Yamada, A., Ohgaki, S., Noda, T., Taniguchi, S.
Safety evaluation of chemicals for use in household products (I). Teratological studies on MITIN LA and 2-mercaptobenzothiazole in mice
Osaka City Inst. Public Health Environ. Sci., 42, 21–29 (1979)

Munro-Ashman, D.
Contact dermatitis from spandex thread
Transactions of the St. John's Hospital Dermatological Society, 52, 131 (1966)

Myhr, B., McGregor, D., Bowers, L., Riach, C., Brown, A.G., Edwards, I., McBride, D., Martin, R., Caspary, W.J.
L5178Y mouse lymphoma cell mutation assay results with 41 compounds
Environ. Mol. Mutagen., 16, 138–167 (1990)

Nagamatsu, K., Kido, Y., Urakubo, G., Aida, Y., Ikeda, Y., Suzuki, Y.
Absorption, distribution, excretion and metabolism of 2-mercaptobenzothiazole in guinea pig
Eisei Kagaku, 25, 59–65 (1979)

Nakamura, A., Ikarashi, Y., Tsuchiya, T., Kaniwa, M.A., Sato, M., Toyoda, K., Takahashi, M., Ohsawa, N., Uchima, T.
Correlations among chemical constituents, cytotoxicities and tissue responses: in the case of natural rubber latex materials
Biomaterials, 11, 92–94 (1990)

Nakamura, A., Momma, J., Sekiguchi, H., Noda, T., Yamano, T., Kaniwa, M., Kojima, S., Tsuda, M., Kurokawa, Y.
A new protocol and criteria for quantitative determination of sensitization potencies of chemicals by guinea pig maximization test
Contact Dermatitis, 31, 72–84 (1994)

Nater, J.P.
Überempfindlichkeit gegen Gummi
Berufsdermatosen, 23, 161–168 (1975)

Nethercott, J.R.
Results of routine patch testing of 200 patients in Toronto, Canada
Contact Dermatitis, 8, 389–395 (1982)

Nethercott, J.R., Holness, D.L., Adams, R.M., Belsito, D.V., De Leo, V.A., Emmett, E.A., Fowler, J., Fisher, A.A., Larsen, W., Maibach, H., Marks, J., Rietschel, R., Rosenthal, L., Schorr, W., Storrs, F., Taylor, J.
Patch testing with a routine screening tray in North America, 1985 through 1989: I. Frequency of response.
Am. J. Contact Dermatitis, 2, 122–129 (1991)

Neubert, D., Kavlock, R.J., Merker, H.J., Klein, J. (eds.)
Risk assessment of prenatally-induced adverse health effects
Springer-Verlag (1992)

Neubert, D.
Personal communication (1993)

Nishioka, K., Murata, M., Ishikawa, T., Kaniwa, M.
Contact dermatitis due to rubber boots worn by Japanese farmers, with special attention to 6-ethoxy-2,2,4-trimethyl-1,2-dihydroquinoline (ETMDQ) sensitivity
Contact Dermatitis, 35, 241–245 (1996)

Novák, M., Kvicalová, E.
Analysis of the results of epicutaneous tests at the dermatological clinic of faculty hospital in Prague 10
Cs. Derm., 60, 305–316 (1985)

NTP (National Toxicology Program)
Toxicology and carcinogenesis studies of 2-mercaptobenzothiazole in F344/N rats and B6C3F1 mice (gavage studies)
NIH Publication No. 88-2588, NTP TR 332 (1988)

NTP (National Toxicology Program)
Comparative toxicology studies in corn oil, safflower oil, and tricaprylin in male F344/N rats as vehicle for gavage
NIH Publication No. 94-3157, NTP TR 426 (1994)

NTP (National Toxicology Program)
Annual plan for fiscal year 1995, p. 64 (1995)

NTP (U.S. National Toxicology Program)
Written communication to BG Chemie of 05.02.1998

Nurse, D.S.
Rubber sensitivity
Austr. J. Derm., 20, 31–33 (1979)

OECD (Organisation for Economic Cooperation and Development, Paris)
OECD Guideline for testing of chemicals no. 406, skin sensitization, adopted by the council on 17th July 1992 (1992)

Ogawa, Y., Kamata, E., Suzuki, S., Kobayashi, K., Naito, K., Kaneko, T., Kurokawa, Y., Tobe, M.
Toxizität von 2-Mercaptobenzothiazol in Mäusen (German translation of the Japanese)
Eisei Shikenjo Hokoku, 107, 44–50 (1989 a)

Ogawa, Y., Kamata, E., Suzuki, S., Kobayashi, K., Kaneko, T., Kurokawa, Y., Tobe, M.
Toxicity of 2-mercaptobenzothiazole (MBT) in mice
J. Toxicol. Sci., 14, 335 (1989 b)

Oleffe, J., Nopp-Oger, M.J., Achten, G.
Batterie européenne de tests épicutanés. Bilan de 300 observations
Berufs-Dermatosen, 20, 209–217 (1972)

Olumide, Y.M.
Contact dermatitis in Nigeria
Contact Dermatitis, 12, 241–246 (1985)

Pecegueiro, M., Brandao, M.
Contact plantar pustulosis
Contact Dermatitis, 11, 126–127 (1984)

Pharmakon Research International, Inc.
Ames Salmonella/microsome plate test
Report, Study No. PH 301-CMA-001-83, PH 301-CMA-001-83A (1984 a)
On behalf of the Chemical Manufacturers Association
NTIS/OTS 0000308 and NTIS/OTS 0510914

Pharmakon Research International, Inc.
CHO/HGPRT mammalian cell forward gene mutation assay
Report, Study No. PH 314-CMA-001-83 (1984 b)
On behalf of the Chemical Manufacturers Association
NTIS/OTS 0000308 and NTIS/OTS 0510914

Pharmakon Research International, Inc.
Genetic toxicology micronucleus test (MNT)
Report, Study No. PH 309A-CMA-001-83 (1984 c)
On behalf of the Chemical Manufacturers Association
NTIS/OTS 0000308 and NTIS/OTS 0510915

Physiological Research Laboratories
Subchronic test report for mercaptobenzothiazole C56519
Report No. 78-60-106002 (1981)
On behalf of Tracor Jitco, Inc.
NTIS/OTS 0206747

Porter, P.S., Sommer, R.G.
Contact dermatitis due to spandex
Arch. Dermatol., 95, 43–44 (1967)

Product Investigations, Inc.
Evaluation of potential hazards by dermal contact
Report, Project No. SH-76-4 (1976)
On behalf of Monsanto Company
NTIS/OTS 0206761

Rajan, V.S., Khoo, R.
Allergic contact dermatitis in Singapore
Mod. Med. Asia, 16, 54–56 (1980)

Randall, D.J., Bannister, R.M.
Acute toxicologic evaluation of mercaptobenzothiazole
Acute Toxic. Data, 1, 62 (1990)

Rannug, A., Rannug, U., Ramel, C.
Genotoxic effects of additives in synthetic elastomers with special consideration to the mechanism of action of thiurames and dithiocarbamates
Industrial Hazards of Plastics and Synthetic Elastomers, 407–419 (1984)

Revazova, Y.A.
Über die mutagene und morphogene Aktivität einiger Bestandteile von Kautschukmischungen (preliminary publication; German translation of the Russian)
Toksikol. Nov. Khim. Veshchestv, Vnedryaemykh Rezin. Shinnuyu Prom., 196–203 (1968)
See also: Chem. Abstr., 71, 47071e (1969)

Rietschel, R.L.
Role of socks in shoe dermatitis
Arch. Dermatol., 120, 398 (1984)

Rodwell, D.E., Gerhart, J.M., Bisinger, E.C., Mercieca, M.D., McKenzie, J.J.
Developmental toxicity study of 2-mercaptobenzothiazole (MBT) in two species
Teratology, 41, 587 (1990)

Rodwell, D.E., Mercieca, M.D., Barnett, J.W., Jr., Murphy, S.J.
Mercaptobenzothiazole (MBT): a dominant lethal evaluation
Toxicologist, 11, 247 (1991)

Roed-Petersen, J., Hjorth, N., Jordan, W.P., Bourlas, M.
Postsorters' rubber fingerstall dermatitis
Contact Dermatitis, 3, 143–147 (1977)

Romaguera, C., Grimalt, F., Vilaplana, J.
Allergic contact dermatitis from shoes: "angry back" without "angry thigh"
Contact Dermatitis, 21, 267 (1989)

Ross, J.B., Obst, D.
Rubber boot dermatitis in Newfoundland: a survey of 30 patients
Can. Med. Assoc. J., 100, 13–19 (1969)

Roul, S., Ducombs, G., Leaute-Labreze, C., Labbe, L., Taieb, A.
Footwear contact dermatitis in children
Contact Dermatitis, 35, 334–336 (1996)

Rudner, E.J.
North American group results
Contact Dermatitis, 2, 208–209 (1977)

Rudner, E.J., Clendenning, W.E., Epstein, E., Fisher, A.A., Jillson, O.F., Jordan, W.P., Kanof, N., Larsen, W., Maibach, H., Mitchell, J.C., O'Quinn, S.E., Schorr, W.F., Sulzberger, M.B.
Epidemiology of contact dermatitis in North America: 1972
Arch. Dermatol., 108, 537–540 (1973)

Rudner, E.J., Clendenning, W.E., Epstein, E., Fisher, A.A., Jillson, O.F., Jordan, W.P., Kanof, N., Larsen, W., Maibach, H., Mitchell, J.C., O'Quinn, S.E., Schorr, W.F., Sulzberger, M.B.
The frequency of contact sensitivity in North America 1972-74
Contact Dermatitis, 1, 277–280 (1975)

Rudzki, E.
Occupational dermatitis among health service workers
Dermatosen, 27, 112–115 (1979)

Rudzki, E., Grzywa, Z.
Contact sensitivity in atopic dermatitis
Contact Dermatitis, 1, 285–287 (1975)

Rudzki, E., Kleniewska, D.
The epidemiology of contact dermatitis in Poland
Br. J. Dermatol., 83, 543–545 (1970)

Rudzki, E., Rebandel, P.
2 cases of dermatitis from rare sources of sensitization to frequent contactants
Contact Dermatitis, 32, 361 (1995)

Rudzki, E., Ostaszewski, K., Grzywa, Z., Kozlowska, A.
Sensitivity to some rubber additives
Contact Dermatitis, 2, 24–27 (1976)

Rudzki, E., Napiórkowska, T., Czerwinska-Dihm, I.
Dermatitis from 2-mercaptobenzothiazole in photographic films
Contact Dermatitis, 7, 43 (1981)

Rudzki, E., Napiórkowska, T., Napiórkowski, W., Stach, E.
Hypersensitivity to mercaptobenzothiazole
Przegl. Dermatol., 69, 383–387 (1982)

Scheuer, B., Rüther, T., v. Bülow, V., Henseler, T., Deing, B., Denzer-Fürst, S., Dreismann, G., Eckstein, L., Eggers, B., Engelke, H., Gärtner, K., Hansen, G., Hardung, H., Heidbreder, G., Hoffmann, E., Kitzmann, H., Kröger, J., Mehnert, I., Möhlenbeck, F., Schlaak, H.E., Schmoll, A., Schmoll, M., Schröder, I., Sipkova, S., Sterry, G., Trettel, W., Walsdorfer, U.
Häufige Kontaktallergene. Eine praxisorientierte Multicenterstudie
Akt. Dermatol. 18, 44–49 (1992)

Schnuch, A., Uter, W., Lehmacher, W., Fuchs, T., Enders, F., Arnold, R., Bahmer, F., Brasch, J., Diepgen, T.L., Frosch, P.J., Henseler, T., Müller, S., Peters, K.P., Schulze-Dirks, A., Stary, A., Zimmermann, J.
Epikutantestung mit der Standardserie. Erste Ergebnisse des Projektes „Informationsverbund Dermatologischer Kliniken“ (IVDK)
Dermatosen, 41, 60–70 (1993)

Schoel, J., Frosch, P.J.
Allergisches Kontaktekzem durch Gummiinhaltsstoffe unter dem Bild einer Pustulosis palmaris
Dermatosen, 38, 178–180 (1990)

Scholes, E.W., Basketter, D.A., Sarll, A.E., Kimber, I., Evans, C.D., Miller, K., Robbins, M.C., Harrrison, P.T.C., Waite, S.J.
The local lymph node assay: results of a final inter-laboratory validation under field conditions
J. Appl. Toxicol., 12, 217–222 (1992)

Schubert, H., Berova, N., Hegyi, E., Jirásek, L., Kalensky, J., Korossy, S., Michailov, P., Nebenführer, L., Prater, E., Rothe, A., Rudzki, E., Temesvari, E., Ziegler, V., Zschunke, E.
Das allergische Kontaktekzem, Analyse einer Stichprobe in fünf sozialistischen Ländern Europas
Dermatol. Monatsschr., 168, 613–623 (1982)

Scientific Associates
Toxicological investigations of 2-mercaptobenzothiazole (Thiotax)
Report (1956)
On behalf of Monsanto Chemical Company
NTIS/OTS 0206761

Scientific Associates (1974)
On behalf of Monsanto Company
Cited in: Farr and Kirwin (1994)

Seifert, H.U., Seifert, B., Wahl, R., Vocks, E., Borelli, S., Maasch, H.J.
Immunglobulin E-vermittelte Kontakturtikaria bzw. Asthma bronchiale durch Latex-enthaltende Haushaltsgummihandschuhe
Dermatosen, 35, 137–139 (1987)

Sertoli, A., Gola, M., Martinelli, C., Angelini, G., Ayala, F., Deledda, S., Goitre, M., Lisi, P., Meneghini, C.L., Pigatto, P., Rafanelli, A., Santucci, B., Schena, D., Valsecchi, R., Zavaroni, C.
Epidemiology of contact dermatitis
Semin. Dermatol., 8, 120–126 (1989)

Shehade, S.A., Beck, M.H., Hillier, V.F.
Epidemiological survey of standard series patch test results and observations on day 2 and day 4 readings
Contact Dermatitis, 24, 119–122 (1991)

Shinoda, M., Ohta, S., Takagi, Y., Akaboshi, S.
Studies on chemical protectors against radiation. XIV. Radiation protective activities of sulfur containing compounds against X-irradiation
Yakugaku Zasshi, 94, 1419–1424 (1974)

Skofitsch, G.
Vom Hund zum Ei? Große und kleine Laboratoriumstiere
In: Lembeck, F. (ed.)
Alternativen zum Tierversuch, p. 71–79
Georg Thieme Verlag Stuttgart, New York (1988)

Song, M., Degreef, H., De Maubeuge, J., Dooms-Goossens, A., Oleffe, J.
Contact sensitivity to rubber additives in Belgium
Dermatologica, 158, 163–167 (1979)

Sorahan, T., Pope, D.
Mortality study of workers employed at a plant manufacturing chemicals for the rubber industry: 1955-86
Br. J. Ind. Med., 50, 998–1002 (1993)

Sorahan, T., Hamilton, L., Jackson, J.R.
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-β-naphthylamine and o-toluidine
Occup. Environ. Med., 57, 106–115 (2000)

SoRI (Southern Research Institute)
Disposition of 2-mercaptobenzothiazole-ring-UL-^{14}C and 2-mercaptobenzothiazole disulfide-ring-UL-^{14}C in Fischer 344 male and female rats dosed orally
Report, SoRI-86-451, Report 5873-I (1986 a)
On behalf of the Chemical Manufacturers Association
NTIS/OTS 0000308-2 and NTIS/OTS 0510971

SoRI (Southern Research Institute)
Disposition of 2-mercaptobenzothiazole-ring-UL-^{14}C and 2-mercaptobenzothiazole disulfide-ring-UL-^{14}C in Fischer 344 male and female rats dosed intravenously
Report, SoRI-86-672, Report 5873-II (1986 b)
On behalf of the Chemical Manufacturers Association
NTIS/OTS 0000308-2 and NTIS/OTS 0510973

SoRI (Southern Research Institute)
Washing efficacy in removal of 2-mercaptobenzothiazole-ring-UL-^{14}C and 2-mercaptobenzothiazole disulfide-ring-UL-^{14}C from Fischer 344 male and female rats and female guinea pigs dosed topically
Report, SoRI-86-1137, Report 5873-IV (1986 c)
On behalf of the Chemical Manufacturers Association
NTIS/OTS 0524621

SoRI (Southern Research Institute)
Disposition of 2-mercaptobenzothiazole-ring-UL-^{14}C in Fischer 344 male and female rats dosed orally after repeated dosing with the unlabeled compound
Report, SoRI-86-1094, Report 5873-III (1987 a)
On behalf of the Chemical Manufacturers Association
NTIS/OTS 0524621

SoRI (Southern Research Institute)
Absorption and disposition of 2-mercaptobenzothiazole-ring-UL-^{14}C and 2-mercaptobenzothiazole disulfide-ring-UL-^{14}C in Fischer 344 male and female rats and female guinea pigs dosed topically
Report, SoRI-86-1200, Report 5873-V (1987 b)
On behalf of the Chemical Manufacturers Association
NTIS/OTS 0521671 and NTIS/OTS 0521675

Spaner, D., Dolovich, J., Tarlo, S., Sussman, G., Buttoo, K.
Hypersensitivity to natural latex
J. Allergy Clin. Immunol., 83, 1135–1137 (1989)

Speit, G.
Der Schwesterchromatidenaustausch als Indikator für genotoxische Effekte
In: Fahrig, R. (ed.)
Mutationsforschung und genetische Toxikologie, p. 263–273
Wissenschaftliche Buchgesellschaft, Darmstadt (1993)

Springborn Laboratories, Inc.
Range-finding teratology study in rats with MBT
Unpublished report, SLS Study No. 3205.1 (1989 a)
On behalf of the CMA Rubber Additives Program Task Group

Springborn Laboratories, Inc.
Teratology study in rats with MBT
Unpublished report, SLS Study No. 3205.2 (1989 b)
On behalf of the CMA Rubber Additives Program Task Group

Springborn Laboratories, Inc.
Range-finding teratology study in rabbits with MBT
Unpublished report, SLS Study No. 3205.3 (1989 c)
On behalf of the CMA Rubber Additives Program Task Group

Springborn Laboratories, Inc.
Teratology study in rabbits with MBT
Unpublished report, SLS Study No. 3205.4 (1989 d)
On behalf of the CMA Rubber Additives Program Task Group

Springborn Laboratories, Inc.
A dominant lethal study in rats with MBT
Unpublished report, SLS Study No. 3205.6 (1989 e)
On behalf of the CMA Rubber Additives MBT Task Group

Springborn Laboratories, Inc.
A preliminary reproduction study in rats with 2-mercaptobenzothiazole (MBT)
Report, SLS Study No. 3205.7 (1989 f)
On behalf of the CMA Rubber Additives MBT Task Group
NTIS/OTS 0518518-1

Springborn Laboratories, Inc.
Two generation reproduction study in rats with MBT
Unpublished report, SLS Study No. 3205.5 (1990)
On behalf of the CMA Rubber Additives Program Task Group

Stables, G.I., Forsyth, A., Lever, R.S.
Patch testing in children
Contact Dermatitis, 34, 341–344 (1996)

Stingeni, L., Lapomarda, V., Lisi, P.
Occupational hand dermatitis in hospital environments
Contact Dermatitis, 33, 172–176 (1995)

Storrs, F.J., Rosenthal, L.E., Adams, R.M., Clendenning, W., Emmett, E.A., Fisher, A.A., Larsen, W.G., Maibach, H.I., Rietschel, R.L., Schorr, W.F., Taylor, J.S.
Prevalence and relevance of allergic reactions in patients patch tested in North America – 1984 to 1985
J. Am. Acad. Dermatol., 20, 1038–1045 (1989)

Strauss, M.E., Barrick, E.D., Bannister, R.M.
Mortality experience of employees exposed to 2-mercaptobenzothiazole at a chemical plant in Nitro, West Virginia
Br. J. Ind. Med., 50, 888–893 (1993)

Sumitomo Chemical Co., Ltd.
Acute oral toxicity of Soxinol M in rats
Unpublished report, PDT-No. C-77-112 (1977)

Sun, C.C.
Two-year experience with patch testing
J. Formosan Med. Assoc., 79, 220–229 (1980)

Suurmond, D., Verspijck Mijnssen, G.A.W.
Allergic dermatitis due to shoes and a leather prothese
Dermatologica, 134, 371–378 (1967)

Syracuse Research Corporation
Technical support document 2-mercaptobenzothiazoles (draft final)
Unpublished report, Contract No. 68-02-4209, Report SCR-TR-85-104 (1985)
On behalf of the Test Rules Development Branch, Existing Chemical Assessment Division, Office of Toxic Substances, Washington, DC, USA

Szybalski, W.
Special microbiological systems: II. Observations on chemical mutagenesis in microorganisms
Ann. N.Y. Acad. Sci., 76, 475–489 (1958)

Takamura, S., Yoshida, J., Suzuki, S.
Effects of various chemical compounds on Ehrlich ascites tumor cells in a maintenance medium
J. Kanazawa Med. Univ., 14, 241–245 (1989)

Tanenbaum, M.H.
Spandex dermatitis
JAMA, 200, 195 (1967)

Trimmer, G.W., Freeman, J.J.
Guinea pig skin sensitization testing of five chemicals using the maximization and closed patch tests
Toxicologist, 8, 129 (1988)

TSCA Existing Chemical Program
2-Mercaptobenzothiazole (MBT)
Document No. AR072-01 – AR072-06 (1991–93)

Turjanmaa, K.
Incidence of immediate allergy to latex gloves in hospital personnel
Contact Dermatitis, 17, 270–275 (1987)

Tuyp, E., Mitchell, J.C.
Scuba diver facial dermatitis
Contact Dermatitis, 9, 334–335 (1989)

Uniroyal Inc.
Product safety data sheet on NaMBT and MBT (1975)
Cited in: Syracuse Research Corporation (1985)

USAF Radiation Laboratory, University of Chicago
A survey of compounds for radiation protection
NTIS No. AD-277 689 (1962)

Vanderbilt Co.
Material safety data sheet 2-mercaptobenzothiazole (1975)
Cited in: Syracuse Research Corporation (1985)

Varelzides, A., Katsambas, A., Georgala, S., Capetanakis, J.
Shoe dermatitis in Greece
Dermatologica, 149, 236–239 (1974)

Veien, N.K., Hattel, T., Justesen, O., Nørholm, A.
Contact dermatitis in children
Contact Dermatitis, 8, 373–375 (1982)

Vestey, J.P., Gawkrodger, D.J., Wong, W.K., Buxton, P.K.
An analysis of 501 consecutive contact clinic consultations
Contact Dermatitis, 15, 119–125 (1986)

Vincze, E., Korossy, S.
Gummihilfsstoffe als Allergene
Dermatosen, 27, 119 (1979)

de Vries, H.R.
Allergic dermatitis due to shoes
Dermatologica, 128, 68–75 (1964)

Vorob'eva, R.S., Mezentseva, N.V.
Vergleichende experimentelle Untersuchung der Toxizität neuer Vulkanisationsbeschleuniger (German translation of the Russian)
Gig. Tr. Prof. Zabol., issue 7, 28–33 (1962)

Wang, X.S., Suskind, R.R.
A study on the structure-activity relationship of morpholine and its derivatives used in the rubber industry. I. A comparison of the sensitizing potency of morpholine and its derivatives in guinea pigs
Toxicologist, 4, 159 (1984)

Wang, X., Suskind, R.R.
Comparison studies of the sensitizing potency of morpholine, 2-mercaptobenzothiazole and two of their derivatives in guinea pigs
Shanghai Yike Daxye Xuebao, 13, 209–212 (1986)

Wang, X., Suskind, R.R.
Comparative studies of the sensitization potential of morpholine, 2-mercaptobenzothiazole and 2 of their derivatives in guinea pigs
Contact Dermatitis, 19, 11–15 (1988)

Wang, X., Tabor, M.W.
A study on the structure-activity relationship of morpholine and its derivatives used in the rubber industry. II. Reactivity of morpholine and its derivatives with select amino acids
Toxicologist, 4, 145 (1984)

Wang, X., Tabor, M.W.
Studies of the reactivity of morpholine, 2-mercaptobenzothiazole and 2 of their derivatives with selected amino acids

Contact Dermatitis, 19, 16–21 (1988)

Warshawshki, L., Mitchell, J.C., Storrs, F.J.
Allergic contact dermatitis from glyceryl monothioglycolate in hairdressers
Contact Dermatitis, 7, 351–352 (1981)

Weisiger, R.A., Jackoby, W.B.
Thiol S-methyltransferase from rat liver
Arch. Biochem. Biophys., 196, 631 (1979)
Cited in: Kloog et al. (1982)

Weston, J.A., Hawkins, K., Weston, W.L.
Food dermatitis in children
Pediatrics, 72, 824–827 (1983)

Wilkinson, D.S., Budden, M.G., Hambly, E.M.
A 10-year review of an industrial dermatitis clinic
Contact Dermatitis, 6, 11–17 (1980)

Wilkinson, S.M., Cartwright, P.H., English, J.S.C.
Allergic contact dermatitis from mercaptobenzothiazole in a releasing fluid
Contact Dermatitis, 23, 370 (1990)

Wilkinson, S.M., Cartwright, P.H., English, J.S.C.
Berufsbedingte Mercaptobenzthiazol-Allergie
Dermatosen, 39, 77 (1991)

Wilson, H.T.H.
Rubber-glove dermatitis
Br. Med. J., 2, 21–23 (1960)

Wilson, H.T.H.
Rubber dermatitis, an investigation of 106 cases of contact dermatitis caused by rubber
Br. J. Dermatol., 81, 175–179 (1969)

Windholz, M., Budavari, S., Blumetti, R.F., Otterbein, E.S. (eds.)
The Merck index
10th ed., p. 838
Merck & Co., Rahway, New Jersey (1983)

Yamaguchi, T., Yamauchi, A., Yamazaki, H., Kakiuchi, Y.
Mutagenicity of rubber additives in tire
Eisei Kagaku, 37, 6–13 (1991)

Young, E., Houwing, R.H.
Patch test results with standard allergens over a decade
Contact Dermatitis, 17, 104–107 (1987)

Younger Laboratories, Inc.
Toxicologic investigation of: Thiotax MBT
Report, Project No. Y-73-288 (1974)
On behalf of Monsanto Company
NTIS/OTS 0206761

Younger Laboratories, Inc.
Toxicologic investigation of: Thiotax powder
Report, Project No. Y-75-237 (1975)
On behalf of Monsanto Company
NTIS/OTS 0206761

Zaitz, I.D.C., Proenca, N.G., Droste, D., Grotti, A.
Dermatite de contato acromiante por sandálias de borracha
Med. Cut. I.L.A., 15, 1–7 (1987)

Zeiger, E.
Mutagenicity of 42 chemicals in Salmonella
Environ. Mol. Mutagen., Suppl. 18, 16, 32–54 (1990)

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., Speck, W.
Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals
Environ. Mutagen., 9, Suppl. 9, 1–110 (1987)

Zeiger, E., Haseman, J.K., Shelby, M.D., Margolin, B.H., Tennant, R.W.
Evaluation of four in vitro genetic toxicity tests for predicting rodent carcinogenicity: confirmation of earlier results with 41 additional chemicals
Environ. Mol. Mutagen., 16, Suppl. 18, 1–14 (1990)

Zhang, X.M., Niklasson, B., Li, S.Y.
Patch testing in cases of eczema and dermatitis in Beijing, China
Contact Dermatitis, 25, 224–229 (1991)

Ziegler, V., Süß, E.
Die allergene Wirkung der Gummiakzeleratoren Tetramethylthiuramdisulfid (TMTD) und Mercaptobenzothiazol (MBT)
Allerg. Immunol. (Leipz.), 20/21, 281–285 (1974/75)

Ziegler, V., Süß, E., Standau, H., Hasert, K.
Der Meerschweinchen – Maximisationstest zum Nachweis der sensibilisierenden Wirkung wichtiger Industrieprodukte
Allerg. Immunol. (Leipz.), 18, 203–208 (1972)

Zina, A.M., Bedello, P.G., Cane, D., Bundino, S., Benedetto, A.
Dermatitis in a rubber tyre factory
Contact Dermatitis, 17, 17–20 (1987)

Includes literature on sensitisation up to 31 January 1997.