Australian Government
Department of Health and Aged Care
Australian Industrial Chemicals Introduction Scheme

Mercaptobenzothiazole and its sodium and zinc salt

Evaluation statement (EVA00173)

31 March 2025

Draft

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AICIS evaluation statement (EVA00173)

Subject of the evaluation

Mercaptobenzothiazole and its sodium and zinc salt

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2(3*H*)-Benzothiazolethione, zinc salt (2:1)	155-04-4
2(3*H*)-Benzothiazolethione, sodium salt (1:1)	2492-26-4

Reason for the evaluation

New information is available about human health risks.

Parameters of evaluation

These chemicals are listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified uses of the chemicals.

These chemicals have previously been assessed including all endpoints under the National Industrial Chemicals Introduction and Assessment Scheme (NICNAS 2016). New information a has become available regarding carcinogenicity and potential public health risks from exposure to rubber products.

Therefore, this evaluation will:

1. review the weight of evidence, including new information, on carcinogenicity
2. consider whether any means for managing risks are required based on the new information.

While this evaluation will provide a summary of other health effects of the chemicals more information on this can be found in the IMAP Assessment for these chemicals (NICNAS 2016).

In this evaluation these chemicals will be referred to as:

- 2-mercaptobenzothiazole (MBT) - (CAS No. 149-30-4)
- zinc mercaptobenzothiazole (ZnMBT) - (CAS No. 155-04-4)
- sodium mercaptobenzothiazole (NaMBT) - (CAS No. 2492-26-4).

Summary of evaluation

Summary of introduction, use and end use

No specific Australian introduction, use and end use information has been identified for MBT and ZnMBT.

The chemical NaMBT has reported commercial use under previous calls for information in Australia (NICNAS 2016).

International use data is expected to be indicative of use patterns in Australia. The chemicals have domestic, commercial and site-limited uses, as well as non-industrial uses.

These chemicals MBT, ZnMBT and NaMBT are used primarily as chemical reaction regulators in the manufacture of rubber articles. Finished rubber products may contain small amounts of unreacted MBT and its salts. The chemicals also function as corrosion inhibitors and may be present in products such as:

- anti-freeze and de-icing products
- lubricants and greases.

Available information indicates use in domestic products is not widespread and at low concentrations.

Human health

Summary of health hazards

Based on the previously assessed data (NICNAS 2016), these chemicals:

- have low acute toxicity via oral, dermal and inhalation routes
- do not cause specific repeat-dose toxicity
- do not cause specific reproductive or developmental toxicity.

The chemical NaMBT is corrosive to the skin, based on animal studies and human case reports (NICNAS 2016). MBT and ZnMBT are not corrosive. The chemicals are known skin sensitisers, with a number of allergic dermatitis cases reported in the literature and positive results in animal studies (NICNAS 2016).

Information on genotoxicity and carcinogenicity has been reviewed as part of this evaluation.

Based on the available data these chemicals are not expected to be genotoxic in vivo. Although in vitro data suggest that these chemicals may cause clastogenic effects in mammalian cells, all available in vivo data were negative.

These chemicals are expected to be carcinogenic based on both an analysis of cancer incidence in workers exposed to MBT and evidence from animal studies. In humans, a positive association between exposure to MBT and bladder cancer has been observed. In animals MBT caused benign and malignant tumours at multiple sites in male and female rats. There is equivocal evidence of carcinogenicity in mice indicated by increased incidences of hepatocellular adenomas or carcinomas (combined).

Hazard classifications relevant for worker health and safety

The chemicals satisfy the criteria for classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This evaluation does not consider classification of physical hazards and environmental hazards. The skin corrosion/irritation classification only applies to NaMBT (CAS No. 2492-26-4) (SWA n.d.). All classifications below are currently listed in the Hazardous Chemical Information System, except for the proposed amendment to carcinogenicity.

Health hazards	Hazard category	Hazard statement
Carcinogenicity	Carc. 1B	H350: May cause cancer
Skin Sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Skin corrosion/irritation	Skin Corr. 1C	H314: Causes severe skin burns and eye damage

Summary of health risk

Public

Based on the available use information, significant public exposure to these chemicals is not expected. Use in domestic products appear to be limited. Any exposure would be further limited by the infrequent use of these products and presence of the chemicals at low concentrations.

A number of rubber consumer products are manufactured using chemicals in this evaluation. Although the chemicals are expected to be chemically bound within the finished articles/products, some unreacted portion of the chemicals may remain, which means some limited consumer exposure may occur. Key exposure scenarios include:

- oral and dermal exposure to rubber granulates in synthetic turf
- daily mouthing of rubber soothers.

Internationally the exposure and subsequent risks of carcinogenicity from these exposure scenarios has been estimated to be low. Based on similar expected exposure scenarios, these risk estimates are considered relevant in Australia.

Therefore, there are no identified risks to the public that require management.

Workers

During product formulation and packaging, dermal and inhalation exposure might occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment.

Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the identified systemic long term health effects, the chemical could pose a risk to workers. Control measures to minimise dermal and inhalation exposure are needed to manage the risk to workers (see **Proposed means for managing risks** section).

Proposed means for managing risk

Workers

Recommendation to Safe Work Australia

It is recommended that Safe Work Australia (SWA) update the Hazardous Chemical Information System (HCIS) to include classifications relevant to work health and safety.

Information relating to safe introduction and use

The information in this statement including recommended hazard classifications, should be used by a person conducting a business or undertaking at a workplace (such as an employer) to determine the appropriate controls under the relevant jurisdiction Work Health and Safety laws.

Control measures that could be implemented to manage the risk arising from dermal or inhalation exposure to these chemicals include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with these chemicals.

Measures required to eliminate or manage risk arising from storing, handling and using these hazardous chemicals depend on the physical form and how these chemicals are used.

These control measures may need to be supplemented with:

- conducting health monitoring for any worker who is at significant risk of exposure to these chemicals if valid techniques are available to monitor the effect on the worker's health.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemicals. Your Work Health and Safety regulator should be contacted for information on Work Health and Safety laws and relevant Codes of Practice in your jurisdiction.

Conclusions

The Executive Director proposes to be satisfied that the identified risks to human health from the introduction and use of the industrial chemical can be managed.

Note:

1. Obligations to report additional information about hazards under *Section 100* of the *Industrial Chemicals Act 2019* apply.
2. You should be aware of your obligations under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory.

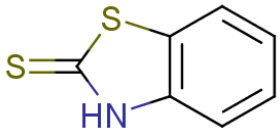
Supporting information

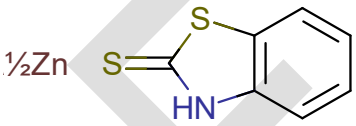
Grouping rationale

The chemicals in this group are: 2(3*H*)-benzothiazolethione (CAS No. 149-30-4), also known at 2-mercaptobenzothiazole (MBT); 2(3*H*)-benzothiazolethione, zinc salt (CAS No. 155-04-4) also known as zinc mercaptobenzothiazole (ZnMBT) and 2(3*H*)-benzothiazolethione, sodium salt (CAS No. 2492-26-4), also known as sodium mercaptobenzothiazole (NaMBT).

MBT is a weak acid that forms salts in basic solutions with a variety of metal ions. The chemicals, NaMBT and ZnMBT hydrolyse to form the parent acid MBT and constituent ions in biological fluids under acidic conditions. The physico-chemical properties of these chemicals are not expected to vary greatly. The systemic toxicity of these chemicals is expected to be similar and will be driven predominantly by MBT and, as such, they are grouped together for human health risk assessment (NICNAS 2016; NTP 1988). Both zinc and sodium are essential metals in humans; therefore, their ions are not expected to cause toxicity except at high doses.

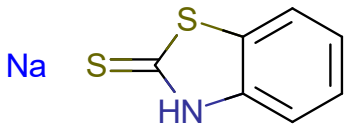
Chemical identity

CAS number	149-30-4
CAS name	2(3*H*)-Benzothiazolethione
Molecular formula	$C_7H_5NS_2$
Associated names	2-Mercaptobenzothiazole (MBT) 1,3-Benzothiazole-2-thiol 2-Sulfanylbenzothiazole
Molecular weight (g/mol)	167.25
SMILES (canonical)	S=C1SC=2C=CC=CC2N1
Structural formula	

CAS number	155-04-4
CAS name	2(3*H*)-Benzothiazolethione, zinc salt (2:1)
Molecular formula*	$C_7H_5NS_2.1/2Zn$
Associated names	Zinc 2-mercaptobenzothiazole (ZnMBT)
	Bis(2-benzothiazolylthio)zinc
	2-Benzothiazolethiol zinc salt
Molecular weight (g/mol)*	399.90
SMILES (canonical)*	[Zn].S=C1SC=2C=CC=CC2N1
Representative structure*	

Additional chemical identity information

* This chemical is a salt and has been represented according to CAS nomenclature/identity conventions.

CAS number	2492-26-4
CAS name	2(3*H*)-Benzothiazolethione, sodium salt (1:1)
Molecular formula*	$C_7H_5NS_2.Na$
Associated names	2-Mercaptobenzothiazole, sodium salt (NaMBT)
Molecular weight (g/mol)*	190.24
SMILES (canonical)*	[Na].S=C1SC=2C=CC=CC2N1
Representative structure*	

Additional chemical identity information

* This chemical is a salt and has been represented according to CAS nomenclature/identity conventions.

Relevant physical and chemical properties

The following information was retrieved from a several sources (CAS n.d.; Chemwatch n.d.; REACH n.d. a-c):

Chemical	MBT	ZnMBT	NaMBT
Physical form	Pale yellow crystalline solid	Pale yellow crystalline solid	Pale yellow crystalline solid
Melting point	180.2–181.7 °C	330 °C	-
Vapour pressure	<2.5 x 10-6 hPa at 25 °C	-	-
Water solubility	118 mg/L at 25 °C	<20.6 mg/L at 20°C	≥100 g/L at 20°C
pK_a	7.03 at 20 °C	7.03 at 20 °C	-
log K_{ow}	2.41	-	-

Introduction and use

Australia

No specific Australian introduction, use and end use information has been identified for MBT and ZnMBT.

NaMBT has reported commercial use under previous calls for information (NICNAS 2016).

International

The following international use information has been identified for the chemicals in this group from the following sources:

- European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers;
- Galleria Chemica (Chemwatch n.d.);
- Government of Canada – Draft screening assessment - Benzotriazoles and Benzothiazoles Group (Government of Canada 2021);
- The International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, 2-mercaptobenzothiazole (IARC 2018);
- the Substances and Preparations in Nordic countries (SPIN) database;
- the US National Library of Medicine's Hazardous Substances Data Bank (HSDB);
- the European Commission Scientific Committee on Consumer Products Report (SCCP 2005);
- National Institute for Occupational Safety and Health Report (NIOSH 2014);
- SmartPractice Denmark, allergen information (SmartPractice DK n.d.);
- the US High Volume Information System (HPVIS) robust summaries on benzothiazole-and morpholine-based thiazoles;

- United States Environmental Protection Agency Chemical Data Reporting (CDR) (US EPA 2016; US EPA 2020).

MBT is a high production chemical in the United States of America (USA). In 2012 the US Environmental Protection Agency (EPA) noted that ~227–454 tonnes/year of MBT were produced, imported, and used in the USA in 2012. In Canada, MBT was introduced at between 10–100 tonnes per annum in 2015.

The chemical and its sodium and zinc salts have broad industrial uses. Their primary use is site-limited as reactants in the vulcanisation process during the manufacture of rubber products. These chemicals also have commercial uses as processing aids in metal production and as corrosion inhibitors. These chemicals may be present in a number of products, including in oils, greases, cutting fluids and cooling/anti-freeze fluids.

Some commercial products containing these chemicals may be used in domestic applications. However, information suggests domestic use is not likely to be widespread. No consumer uses were reported in REACH dossiers or as part of US EPA chemical data reporting requirements. In North American product databases NaMBT has reported domestic use as an ingredient in automotive products (radiator cleaner at 1.0–1.5%).

These chemicals may be present in any product containing rubber elements. These include shoes, gloves, clothing, swimming costumes, swim caps, support stockings, injury support wraps, condoms, dental dams and mouth guards.

MBT is reported to be used in commercial automotive products, including in brake pads and tyres. MBT is expected to be present in rubber vehicle tyres at ~1% (OECD 2004). These chemicals may also be present in recycled tyres used to create rubber granulates/pellets with various downstream uses. One of which is use in artificial turf pitches to soften and reduce impact for users (Government of Canada 2021; RIVM 2017). Recycled tyres may also be used as flooring in sport centres/playgrounds and other settings (Government of Canada 2021).

These chemicals have no reported cosmetic use.

These chemicals have reported non-industrial uses, including in veterinary products; as fungicides and pesticides.

Existing Australian regulatory controls

AICIS

No specific controls are currently available for these chemicals.

Public

No specific controls are currently available for these chemicals.

Workers

These chemicals are listed in the Hazardous Chemical Information System HCIS (Safe Work Australia, SWA) with the following hazard categories and statements for human health. The skin corrosion/irritation classification only applies to NaMBT (CAS No. 2492-26-4) (SWA n.d.).

Health hazards	Hazard category	Hazard statement
Skin Sensitisation	Skin Sens. 1	H317: May cause an allergic skin reaction
Skin corrosion/irritation	Skin Corr. 1C	H314: Causes severe skin burns and eye damage

There are no specific exposure standards available for these chemicals in Australia (SWA n.d.).

International regulatory status

Exposure standards

The following Protective Action Criteria (PAC) (formerly known as temporary emergency exposure limits (TEELs) have been recommended by the United States Department of Energy for MBT (Chemwatch n.d.):

- 15 mg/m^3 (PAC-1)
- 27 mg/m^3 (PAC-2)
- 56 mg/m^3 (PAC-3).

Human exposure

Public

Use of these chemicals in domestic products such as lubricants/grease and de-icing products appear to be limited. Any public exposure would be further limited by the infrequent use of these products and the presence of the chemicals at low concentrations.

Limited exposure to MBT may occur through exposure to consumer goods containing rubber. One route of exposure of potential concern is dermal and oral exposure in children using rubber pacifiers (soothers) and bottle nipples/teats. The chemical was detected in only 1 of 19 natural rubber products tested in a Dutch retail survey, with migration considerably lower than the limit of 0.3 mg/teat (Bouma et al. 2003). In 2018 a Health Canada study on rubber soothers available on the Canadian market (n=20) did not find any MBT above the 10 mg/kg limit of quantification (LOQ) (Government of Canada 2021).

Tyre products containing MBT are recycled and reused in a number of products, including as granulates/pellets used to soften artificial turfs and reconstituted as children's playgrounds. Dermal and oral exposure (through ingestion of granules) can occur. The highest exposure scenarios were identified as mouthing of rubber granules by a toddler and dermal exposure from playing on synthetic turf by a child. The potential oral exposure to MBT from rubber

granulates made from recycled tyres was estimated to be 9.8×10^{-5} mg/kg bw/(day) and the dermal exposure is estimated to be 2.5×10^{-3} mg/kg bw/(day). This is based on the maximum reported concentration of 7.6 mg/kg MBT in a synthetic turf pitch found in the Netherlands (Government of Canada 2021; RIVM 2017).

MBT has also been shown to leach out from rubber products into water or acidic foods after 24 hours of contact (EC 2005); however, exposure from use in food packaging is expected to be negligible (Government of Canada 2021).

Health hazard information

This evaluation reviews available data for MBT and 2 of its salts relating to carcinogenicity. More information on other endpoints not considered in this evaluation are available in the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework report conducted under the former scheme, the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (NICNAS 2016).

Toxicokinetics

Based on the molecular weights and log Kow values (see **Relevant physical and chemical properties**), chemicals in this group are expected to be readily absorbed following oral and dermal exposure. Based on vapour pressures, inhalation exposure is not expected unless dusts/aerosols are formed. The absorption, distribution, metabolism and excretion of MBT has been studied in several species.

In a study in guinea pigs using radiolabelled MBT, absorption was observed to occur via the skin. Absorption increased when the skin was abraded (REACH n.d.-a).

Following subcutaneous injection, distribution was found to occur primarily to the kidneys, liver and thyroid. Within 6 hours of injection 90% of the compound was conjugated with glucuronides and sulfates, and excreted in the urine (REACH n.d.-a).

The following metabolites of MBT have been identified in rats and guinea pigs: benzothiazole-2-glutathione, benzothiazole-2-mercapturic acid, benzothiazole-2-mercaptan, benzothiazole-2-mercapto glucuronide or as inorganic sulfate (REACH n.d.-a).

Male and female rats orally administered radiolabelled MBT excreted 90.7 and 101% of the dose, respectively (96 hours after administration). In the same time period, 10 and 5.3% of the administered dose was excreted via the faeces in males and females, respectively. The study showed that some radioactivity (1.2 to 1.5%) of the dose was not excreted within the 96 hour time point. This portion of the dose remained associated with erythrocyte membranes (REACH n.d. -a). The half-life of MBT has been reported as <8 hours and as short as 4–6 hours in F344 rats (NAP 2004).

Following dermal application of radiolabelled MBT to guinea pigs, the chemical was distributed to the blood compartment and internal organs, with the most radioactivity identified in the thyroid. Some radioactivity was also identified in the lungs, kidneys and liver to lesser extents (NAP 2004).

Observation in humans

In a small pilot study conducted in preparation for a large, 10 year study by the German government, an analytical method for detection of MBT and its metabolites in urine was

developed. The study demonstrated that MBT was excreted in the urine of 4 workers exposed to the chemical, thus indicating absorption had occurred. The chemical was excreted mainly as conjugates (e.g. 2-mercaptobenzothiazole glucuronide) rather than in its unchanged form (Gries et al. 2015).

Genotoxicity

Based on the available data, these chemicals are not expected to be genotoxic in vivo. Although in vitro data suggest that these chemicals may cause clastogenic effects in mammalian cells, all available in vivo data are negative.

In vitro

- In an Ames test (bacterial reverse mutation assay), MBT was negative in *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 up to a maximum concentration of 300 µg/plate, with and without metabolic activation (REACH n.d.-a)
- An Ames test with MBT was negative in *S. typhimurium* strains TA 100, TA 1535 and TA 1537 at concentrations up to 10,000 µg/plate. Strain TA 98 had equivocal and weakly positive results at doses ≥333 µg/plate with metabolic activation (US EPA 2016).
- In an Ames test, NaMBT was negative in *S. typhimurium* TA 98, TA 100, TA 1535, TA 1537 and TA 1538 strains at concentrations up to 5 µL/plate with and without metabolic activation (REACH n.d. -c)
- In an Ames test, ZnMBT was negative in *S. typhimurium* TA 1535, TA 1537, TA 98, TA 100 and TA 102 strains at concentrations up to 5000 µg/plate, with and without metabolic activation (REACH n.d.-b)
- MBT was negative in a non-guideline gene mutation assay in fungi (D4 strain), when tested at up to 500 µg/plate, with and without metabolic activation. No further experimental details were provided (REACH n.d. -a)
- In a mammalian chromosomal aberration test in Chinese hamster ovary (CHO) cells, MBT was tested at up to 0.6 µg/mL. The chemical was negative without metabolic activation and inconclusive with metabolic activation (REACH n.d. -a)
- In a mammalian chromosomal aberration test in CHO cells a significant increase in chromosomal aberrations was observed at 351-451 µg/mL in the presence of metabolic activation. No significant induction of chromosomal aberrations in absence of activation (NTP 1988)
- In a mouse lymphoma assay MBT induced mutations at the Tk+/– locus in mouse L5178Y lymphoma cells in the presence of S9 metabolic activation (at concentrations up to 20 µg/ml). The chemical was negative without metabolic activation (at up to 150 µg/ml) (REACH n.d. -a; NTP 1988)
- In a mouse lymphoma assay, MBT (at concentrations up to 100 µg/mL) was tested in mouse lymphoma L5178Y cells. No significant increases in mutant frequency were observed at any tested concentration, with and without metabolic activation (REACHa).
- MBT induced polyploidy in Chinese hamster lung (CHL) cells in the presence and absence of a metabolic activation system (Matsuoka et al. 2005)
- In a sister chromatid exchange (SCE) assay, MBT induced a relative increase in SCE's in CHO cells in the presence of metabolic activation. However, the chemical induced significant cell cycle delay and no dose-response relationship was observed (REACH n.d.-a; NTP 1988).

- ZnMBT induced an increase in micronuclei formation in cultured human peripheral blood lymphocytes. A statistically significant linear trend was observed in all treatments, indicating a positive result (REACH n.d. -b).
- MBT did not induce micronucleus formation in human gastric and lung carcinoma cell lines (MGC-803 and A549, respectively) (IARC 2018)

In vivo

- In a mouse micronucleus assay, MBT was tested in CD-1 mice (4 animals/sex) at 300 mg/kg bw/day once or twice, via intraperitoneal administration. No increase in micronuclei formation was reported (REACH n.d.-a; REACH n.d.-b)
- In a chromosome aberration assay, Swiss albino mice (4 animals/sex/dose) were administered ZnMBT at 0, 24, 43 or 96 mg/kg bw/day by a single intraperitoneal injection. The chemical had no effect on structural chromosomal aberration in the treatment groups (REACH n.d.-c)
- In a gavage study with male and female Fischer 344 rats, MBT (single administration of 375 mg/kg bw) did not bind to DNA in any of the tissues examined (liver, adrenals, pituitary gland, pancreas, and bone marrow) (IARC 2018)
- In a dominant lethal assay, SD rats (28 males/group) were dosed with MBT at 0, 220, 770 or 1300 mg/kg bw/day and then mated to unexposed females. No statistically significant or dose-related increase in embryonic deaths were reported (no dominant lethal effect) (US EPA 2016).

In silico

Based on the mechanistic profiling functionality of the OECD QSAR Toolbox, structural alerts for in ‘vitro chromosome aberration’ and ‘cytogenicity/chromosome aberration study in mammalian cells’, were identified for MBT. ZnMBT and NaMBT were out of domain for QSAR genotoxicity predictions. General mechanistic alerts were identified for DNA binding for MBT, ZnMBT and NaMBT (thiols, reactive oxygen species formation) (OECD QSAR Toolbox version 4.2). No structural alerts for genotoxicity (in vitro or in vivo) were produced for MBT using OASIS–TIMES (Optimised Approach based on Structural Indices Set–Tissue Metabolism Simulator; version 2.31.2). No structural alerts for genotoxicity were produced for MBT using the expert rule-based system, DEREK (Deductive Estimation of Risk from Existing Knowledge) Nexus (version 2.2), (Lhasa Limited n.d.’ OASIS LMC n.d.).

Carcinogenicity

Based on the weight of evidence, including human studies, these chemicals are considered to be carcinogenic. In humans, a positive association between exposure to MBT and bladder cancer has been observed. In animals, MBT caused benign and malignant tumours as indicated by increased incidences of hepatocellular adenomas or carcinomas (combined). Hazard classification is warranted.

The IARC has classified MBT as a Group 2A carcinogen, i.e. “probably carcinogenic to humans” based on limited evidence in human data and sufficient evidence in animal studies (IARC 2018).

Animal data

In a GLP compliant 2 year carcinogenicity study conducted according to OECD TG 451 (carcinogenicity studies), F344/N rats (50 animals/sex/dose) were orally administered MBT at doses of 0, 375 or 750 mg/kg bw/day for males, and 0, 188 or 375 mg/kg bw/day for females

for 5 days/week (NTP 1988). Noteworthy tumour/lesion incidence (overall rates) has been reported for males and females in tables 1 and 2, respectively. Historical control data from NTP studies has been included where available. Increased incidences of mononuclear cell leukemia, pancreatic acinar cell adenomas, adrenal pheochromocytomas or malignant pheochromocytomas (combined), and preputial gland adenomas or carcinomas (combined) were observed in the exposed males. Increased incidences of adrenal pheochromocytomas and pituitary gland adenomas or carcinomas (combined) were also observed in exposed females. Low incidences of transitional cell papillomas of the renal pelvis and a transitional cell carcinoma of the renal pelvis were observed in exposed males. Tumour incidence was not always dose related. For example, mononuclear cell leukemia and pancreatic acinar cell adenomas in male rats were increased only in the low dose groups. Mononuclear cell leukaemia has high spontaneous tumour incidence in F344 rats. Dose-related trends were observed for pituitary gland adenomas in female rats and adrenal pheochromocytomas in males and females. Although adrenal pheochromocytoma and pituitary adenoma have high spontaneous tumour incidence in male F344 rats, incidence rates were above historical controls and tumours were observed in both sexes.

Table 1 Incidence of neoplastic lesions in F344/N male rats

Tumour type	0 mg/kg bw/day	375 mg/kg bw/day	750 mg/kg bw/day	Historical control
Mononuclear cell leukemia	7 (14%)	*16 (32%)	3 (6%)	202/1450 (14%)
Pituitary gland hyperplasia	10 (20%)	17 (34%)	12 (25%)	-
Pituitary gland adenoma	14 (28%)	*24 (42%)	12 (25%)	344/1411 (24%)
Medullary hyperplasia	9 (18%)	14 (28%)	10 (20%)	-
Pheochromocytoma	18 (36%)	*25 (50%)	*22 (45%)	-
Malignant pheochromocytoma	0 (0%)	2 (4%)	2 (4%)	-
Pheochromocytoma or malignant Pheochromocytoma	18 (36%)	27 (54%)	24 (49%)	347/1442 (24%) combined pheochromocytoma and malignant pheochromocytoma
Pancreatic acinar cell hyperplasia	5 (10%)	15 (30%)	7 (14%)	-
Pancreatic acinar cell adenoma	2 (4%)	*13 (26%)	6 (12%)	80/1381 (6%)
Preputial gland hyperplasia	0 (0%)	0 (0%)	1 (2%)	-
Preputial adenoma or carcinoma	1 (2%)	6 (12%)	5 (10%)	65/1450 (4%)
Mesotheliomas	0 (0%)	2 (4%)	3 (6%)	55/1450 (4%)
Fibroma, neurofibroma, sarcoma or fibrosarcoma	3 (6%)	6 (12%)	7 (14%)	126/1450 (9%)
Kidney/pelvis epithelial hyperplasia/transitional cell papilloma or carcinoma	0 (0%)	6 (12%)	2 (4%)	-
Kidney/tubule focal hyperplasia	0 (0%)	3 (6 %)	3 (6 %)	-
Kidney tubular cell adenoma	0 (0%)	1 (2 %)	1 (2 %)	-

*Statistical significance compared with vehicle control

Table 2 Incidences of neoplastic lesions in F344/N female rats

Tumour type	0 mg/kg bw/day	188 mg/kg bw/day	375 mg/kg bw/day	Historical control
Mononuclear cell leukemia	6 (12%)	14 (28%)	9 (18%)	271/1450 (19%)
Pituitary gland hyperplasia	8 (16%)	10 (20%)	6 (12%)	-
Pituitary adenoma	15 (31%)	*24 (48%)	*25 (50%)	344/1411 (24%)
Pituitary adenocarcinoma	1 (2%)	0 (0%)	0 (0%)	561/1407 (40 %)
Medullary hyperplasia	5 (10%)	8 (16%)	2 (4%)	-
Pheochromocytoma	1 (2%)	**5 (10%)	**6 (12%)	82/1443 (6%)
Kidney/pelvis epithelial hyperplasia/transitional cell papilloma or carcinoma	1 (2%)	0 (0 %)	0 (0 %)	-
Kidney/tubule focal hyperplasia	1 (2%)	0 (0 %)	0 (0 %)	-
Kidney tubular cell adenoma	0 (0 %)	0 (0 %)	0 (0 %)	-

*Statistical significance compared with vehicle control

**Statistical significance in survival-adjusted rates compared with vehicle control

A parallel study was conducted according to OECD TG 451 in B6C3F1 mice (50 animals/sex/dose). Animals were orally administered MBT at 0, 375 or 750 mg/kg bw/day, 5 days per week for 103 weeks. Noteworthy tumour/lesion incidence (overall rates) in females are presented in table 3 below. Historical control data from NTP studies have been included where available. A significantly increased incidence of hepatocellular adenoma or carcinoma (combined) in female mice was reported at the lowest dose. The low survival rate in the high dose group of female mice may have reduced expression of tumourigenicity as this type of neoplasm occurs later in mice. MBT did not result in any significant increase in tumour incidence in males (NTP 1988; REACH n.d.-a).

Table 3 Incidences of neoplastic lesions in B6C3F1 female mice

Tumour type	0 mg/kg bw/day	375 mg/kg bw/day	750 mg/kg bw/day	Historical control
Hepatocellular adenoma	3 (6%)	7 (14%)	4 (8%)	-
Hepatocellular carcinoma	1 (2%)	5 (10%)	0 (0%)	-
Hepatocellular adenoma and carcinoma combined	4 (8%)	*12 (24%)	4 (8%)	116/1489 (8%) combined hepatocellular adenoma and carcinoma
Pituitary hyperplasia	16 (33%)	14 (29%)	12 (24 %)	-
Pituitary adenoma	20 (41%)	11 (22%)	3 (6%)	-
Pituitary carcinoma	1 (2%)	0 (0%)	0 (0%)	257/1324 (19%) combined adenomas or carcinomas
Malignant lymphoma	19 (38%)	10 (20%)	6 (12%)	393/1494 (26%) combined lymphomas and leukemias

*Statistical significance compared with vehicle control

In a non-guideline study conducted with B6C3F1 and B6AKF1 mice (18 animals/sex), MBT was administered once by subcutaneous injection at 1000 mg/kg bw (equivalent to 323 ppm). No increase in tumour incidence was reported and no adverse treatment-related effects were observed (REACH n.d.-a).

In a non-guideline study in B6C3F1 and B6AKF1 mice (18 animals/sex), MBT was orally administered at 100 mg/kg bw (equivalent to 323 ppm). No statistically significant differences in tumour incidence was reported in either mouse strain. No adverse treatment-related effects were observed (REACH n.d.-a).

In a non-guideline study in B6C3F1 and B6AKF1 mice (18 animals/sex), MBT was administered once by subcutaneous injection at 1000 mg/kg bw. An increase in the incidence of reticulum cell sarcoma was noted in B6CF31 male mice. The total number of males with tumours and the incidences of hepatoma and pulmonary adenomas and carcinomas were not increased compared with controls (REACH n.d.-a).

In a non-guideline carcinogenicity study, Slc:ddY mice (30/sex/dose) were orally administered MBT at 0, 30, 120, 480 or 1920 ppm (equivalent to 3.6, 14.69, 57.90 and 289.4 mg/kg bw/day for males, and 0, 3.61, 13.52, 58.87and 247.98 mg/kg bw/day for females, respectively) for 20 months. No substance-related tumours were reported. Haematological changes were reported in males at the highest dose (REACH n.d.-a).

In a study conducted with B6C3F1 and B6AKF1 mice (18 animals/sex), ZnMBT was administered once by oral gavage at 1000 mg/kg bw (equivalent to 3385 ppm). Animals did not show any increase in tumour incidence compared with controls (REACH n.d.-b).

In a non-guideline carcinogenicity study, NaMBT was administered to rats (strain not specified) (10/sex/dose) at 0, 12, 37.9 or 120 ppm in their feed (approximately equivalent to 0, 0.6, 1.9 and 6.0 mg/kg bw/day) for 2 years. No carcinogenic effect was reported. No other study details were reported (REACH n.d.-c).

In a parallel study, NaMBT was administered to dogs (strain not specified) (3/dose) at 0, 12, 37.9 or 120 ppm in the feed (approximately equivalent to 0, 0.3, 0.9 or 3.0 mg/kg bw/day) for 3 years. No carcinogenic effect was reported. No other study details were reported (REACH n.d.-c).

Observation in humans

A set of studies conducted with workers from a chemical manufacturing plant in Wales, United Kingdom provides insights into MBT exposure and cancer in humans (Sorahan & Pope 1993; Sorahan 2008; Sorahan 2009; Sorahan et al. 2000).

The studies considered chemical exposure in a cohort of 2160 male workers from 1955–2005. In the chemical production plant, MBT was manufactured along with vulcanisation inhibitors and accelerators, antioxidants, and many other proprietary products for the rubber industry. NaMBT and ZnMBT were involved in operations at the plant, as were a number of other chemicals, including aniline, phenyl-β-naphthylamine, ortho-toluidine, and polymerized 2,2,4-trimethyl1,2-dihydroquinoline (Sorahan et al. 2000) The different types of work processes at the plant dictated the levels of exposure to MBT and other chemicals. The highest exposures to MBT were reported to be 11.7 mg/m^3 for day pack and pellet operators, and 8.5 mg/m^3 for bag flake operators and daymen (Sorahan et al. 2000).

The 2008 study focused on MBT exposure in workers, the incidence of urinary bladder cancer and associated mortality and morbidity. Investigators found that MBT exposure was associated with an excess in mortality (8 deaths; standardised mortality ratio, 3.74; 95% CI, 1.62–7.37) and incidence (12 cases; standardised relative risk, 2.53; 95% CI, 1.31–4.41) compared with relevant controls (national rates) (Sorahan 2008).

The IARC performed an internal multivariate analysis of bladder cancer incidence using the full cohort of workers. The investigators found a positive, non-significant trend (P=0.16) with cumulative exposure to MBT (when adjusted for age, calendar period, and duration of employment with exposure to other chemicals produced in the plant (ortho-toluidine, aniline, and phenyl-β-naphthylamine)) (IARC 2018).

One study specifically evaluated worker mortality (1955–2005) and morbidity (1971–2005) associated with non-urinary bladder cancers in a cohort of 363 male production workers exposed to MBT (Sorahan 2009). Incidence of a range of cancers were calculated and compared with national mortality and cancer incidence rates. Investigators reported that this cohort of MBT exposed workers showed significantly increased incidences of multiple myeloma and cancers of the large intestine and lung (albeit the latter was only of borderline significance).

The following were reported for those exposed to MBT:

- Colorectal cancer: 8 deaths (standardised mortality ratio (SMR), 2.32; 95% CI, 1.00–4.57) and 9 diagnoses (standardised relative risk (SRR), 1.81; 95% CI, 0.83–3.44)

- Lung cancer: 27 deaths (SMR, 1.38; 95% CI, 0.91–2.01) and 26 diagnoses (SRR, 1.52; 95% CI, 0.99–2.23)
- Multiple myeloma: 3 deaths (SMR, 4.40; 95% CI, 0.91–12.87) and 4 diagnoses (SRR, 4.65; 95% CI, 1.27–11.91) (Sorahan 2009)

The IARC performed an internal multivariate analysis of colorectal cancer incidence related to MBT exposure in the full cohort of subjects. The investigators found that the significant increasing trend in colorectal cancer incidence was still present with cumulative exposure to MBT when adjusted for duration of employment with exposure to ortho-toluidine, aniline and phenyl-β-naphthylamine (IARC 2018).

In a follow up to a previous study, the carcinogenic potential of MBT was assessed in a cohort of 1059 white male rubber chemicals plant workers in West Virginia, USA. Investigators assessed exposure to MBT and 4-aminobiphenyl (PAB) (an IARC Group 1 carcinogen, classified for causing urinary bladder cancers) and the development of lung, prostate and bladder cancers. The cohort was split as follows: MBT workers who had been exposed to PAB, MBT workers with potential exposure to PAB and MBT workers with no known exposure to PAB. It was found that MBT workers had normal incidence rates of lung (SMR = 1.0 95% confidence interval (95% CI) 0.7 to 1.5) and prostate (SMR=0.9, 95% CI 0.2 to 2.3) cancer. Among the 511 MBT exposed workers with no documented exposure to PAB, a 4-fold statistically significant excess of mortality from bladder cancer was reported. A statistically significant trend in mortality from urinary bladder cancer with increasing cumulative exposure to MBT was also observed. However, the manufacturing processes for MBT and PAB overlapped for 20 years of the study period. Therefore, the investigators noted the potentially confounding exposure of a known bladder carcinogen to MBT exposed workers which makes definitive risk evaluation of bladder cancer difficult in this population (Collins et al 1999).

In silico

Based on the mechanistic profiling functionality of the OECD QSAR Toolbox, structural alerts for in ‘carcinogenicity – undefined route of administration’ were identified for MBT, ZnMBT and NaMBT (OECD QSAR Toolbox version 4.2).

Mechanistic studies

The mechanism by which MBT and its salts exert their carcinogenic effect is not well characterised. Although results in in vitro genotoxicity studies (see **Health Hazards – Genotoxicity** section) show some positive results, there is no evidence that the chemical is genotoxic in vivo.

There is moderate evidence that MBT exerts a carcinogenic effect via modulating receptor-mediated events. A study in mouse hepatoma cells showed that MBT stimulated aryl hydrocarbon receptor (AhR)-DNA binding and AhR-dependent gene expression (He et al. 2011). AhR activation can lead to various processes which may contribute to carcinogenesis, such as cellular proliferation, migration, and inhibition of apoptosis (Griffith et al. 2024). Additionally, MBT upregulates MMP1 expression, a cancer metastasis biomarker, via the same mechanism (Zhang et al. 2022).

Weak evidence indicates that MBT may exert carcinogenic effects by interfering with thyroid function. It inhibits thyroid peroxidase in rat and pig cells, an enzyme whose absence is linked to certain cancers (Paul et al. 2013). MBT also disrupts thyroid hormones in African clawed frog (*Xenopus laevis*) larvae. The proposed effects are supported by a study showing

inhibition of thyroid peroxidase derived from pig thyroid glands, and the inhibition of thyroxine release in a *X. laevis* thyroid gland ex vivo culture system (Hornung et al. 2015).

Human health risk characterisation

Critical health effects

The critical health effect for risk assessment in this evaluation is carcinogenicity.

Public risk

Internationally, the risks to the public resulting from exposure to rubber products containing these chemicals has been estimated. Based on similar expected exposure scenarios, these risk estimates are considered relevant in Australia.

The Government of Canada estimated the risks of exposure to MBT from:

- mouthing of rubber granulates from a synthetic turf by a toddler
- dermal exposure from playing on a synthetic turf by a child
- daily mouthing of soothers containing MBT at concentrations up to the LOQ (10 mg/kg rubber).

The cancer risk (number of expected cases attributable to a specific risk factor) associated with daily mouthing of soothers containing MBT at this level was calculated to be 1.1×10^{-6}. The lifetime average daily dose of MBT resulting from the daily mouthing of soothers, together with exposure to MBT in rubber granulates was estimated to be 4.9×10^{-3}, resulting in a cancer risk of 3.1×10^{-6} (Government of Canada 2021). Overall, the cancer risk from these exposure scenarios was estimated to be very low.

The National Institute for Public Health and the Environment (RIVM) in the Netherlands evaluated potential human exposure to MBT and the associated risk resulting from the use of recycled tyres in synthetic sports fields. They evaluated a number of exposure scenarios, including mouthing of rubber granulates in toddlers, dermal absorption in children and lifetime exposure. In all assessed scenarios, the investigators reported no significant risk based on calculated exposures compared with the exposure limit regarded as safe (RIVM 2017).

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