SUBSTANCE EVALUATION REPORT

Public Name: Benzothiazole-2-thiol (2-MBT)

EC Number(s): 205-736-8

CAS Number(s): 149-30-4

Submitting Member State Competent Authority:

BAuA
Federal Institute for Occupational Safety and Health
Division 5 - Federal Office for Chemicals
Friedrich-Henkel-Weg 1-25
D-44149 Dortmund, Germany

Year of evaluation (as given in the CoRAP): 2013

VERSION NUMBER: 1.2 **DATE: June 2014**

Conclusions of the most recent evaluation step	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	
Concern clarified; Need for risk management measures; RMO analysis to be performed	x
Other:	

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Executive summary

Grounds for concern

- Initial concern:
  Human health/CMR; Sensitiser; Exposure/Wide dispersive use; Consumer use; Exposure to sensitive populations; Aggregated tonnage.

- Initial concern justification:
  2-MBT is used as an accelerator for the vulcanisation of rubber. The substance is self-classified by some notifiers as Carc. 1B. In Germany the expert committee for occupational exposure values has identified the substances as possible carcinogen. The substance evaluation is intended to clarify whether the available data justify a harmonised classification regarding carcinogenicity and/or genotoxicity.
  On the basis of test results on the release of 2-MBT from consumer products (air mattresses) and the maximum possible dermal uptake of the substance, in an evaluation by the Federal Institute for Risk Assessment (BfR) it was found that the emission of 2-MBT from consumer products should be minimised as far as possible. The analysis of migration rates of 2-MBT from air mattresses under realistic conditions revealed that the safety margin between the possible dermal up-take (under worst-case exposure assumptions) and the NOAEL may be below 100 so that a preventive consumer protection is considered necessary. The substance evaluation is intended to clarify whether risks from this use and possible other uses of the 2-MBT in consumer products arise.

- No additional concern has been identified.

Procedure

Cursory evaluation of the human health related toxicity profile of 2-MBT including the available Points of Departure (PoDs) and Derived No-Effect Levels (DNELs) was performed from April 2013 to November 2013. This assessment focused on the evaluation of the endpoints sensitization, mutagenicity and carcinogenicity.

The consumer uses and consumer exposure resulting thereof has been evaluated based on the information given by the registrants in the registration dossiers and Chemical Safety Reports as well as information taken from open data bases, academic literature and European national product registers. Registration data available by November 2013 has been assessed. They were checked and verified against the information taken from other sources. Risk characterisation for consumers was carried out in November 2013.

Conclusions

For workers and the environment no concern was identified, however only a cursory evaluation was performed.

The currently available data as presented in the registration dossier and as supplemented during this process is sufficient for the evaluation and assessment of the human health related toxicity profile of 2-MBT. No additional toxicologically relevant concern was identified. The concern on any need for harmonised classification and labelling of 2-MBT regarding carcinogenicity and/or genotoxicity is clarified. The available data are sufficient and appropriate to conclude that there is no need for a proposal for harmonised classification and labelling.

The consumer exposure resulting from the use of the substance as vulcanisation agent for rubber articles has been assessed transparently in the registration dossier. No further information on consumer exposure from the registrant is needed to clarify the concern.

However, with regard to the total extent of consumer exposure emanating from the use of such articles, it needs to be noted that use of other vulcanisation agents than 2-MBT (e.g. N-cyclohexyl-2-benzothiazole sulphonamide and 2-Mercaptobenzothiazyl disulfide) may also release 2-MBT during their intended use.

The exposure assessment performed by the registrants indicates the level of dermal consumer exposure to the substance due to the use of 2-MBT to be of the same magnitude as from the detectable amounts published in literature to migrate from some consumer products. However, from the available information the evaluating MSCA concludes that this exposure is not negligible in all cases. To assess if risks arising from the use of 2-MBT as vulcanisation agents for consumer articles made of rubber or containing rubber parts are adequately controlled, the risk characterisation ratios were calculated on the basis of the exposure estimates of the registrants and the DNELs derived by the eMSCA. With regard to possible systemic toxic effects the health risks arising via the oral, dermal and inhalative routes of exposure from consumer use of consumer articles made of rubber or containing rubber parts proved to be sufficiently controlled (RCR < 1).

However, 2-MBT is a skin sensitising chemical, a property, which is generally regarded as a threshold effect. But based on the available human and experimental data it was not possible to derive a DNEL to compare it with exposure levels resulting from the use of 2-MBT in consumer products. Hence, no risk characterisation ratio can be determined and the level of risk for skin sensitisation and/or allergic skin reactions cannot be estimated.

To assess the exposure of the general public to 2-MBT biomarkers have been identified and the substance will be taken up into biomonitoring programs The choice of further regulatory measures will be dependent on the results of this programs and on cases of sensitisation of consumers/ of the general public identified e.g. by the Information Network of Departments of Dermatology (IVDK). If based on these results exposure of the general population and cases of contact allergy to 2-MBT in consumers are evident, further action is considered necessary and the evaluating Members State will perform a risk management option analysis (RMOA).

Regarding the health risks for consumers arising from the skin sensitising properties of 2-MBT and the occasion of dermal exposure via use of articles made of rubber or containing rubber parts there is a need to consider risk management measures for consumers. Possible options for risk management include restriction or other Community wide measures. Under restriction it would in principle be possible to cover the various sources for 2-MBT release into consumer articles, i.e. to include also other vulcanisation agents that release 2-MBT during their use. Since currently the risk of skin sensitisation/allergic reactions for consumers from 2-MBT or substances releasing 2-MBT cannot be substantiated and for a restriction process the proportionality of the envisaged action needs to be considered, further information is considered necessary. A discussion of a restriction as a regulatory option will be included in the envisaged RMOA by the evaluating member state after the results of the monitoring programme are available.

SVHC identification and subsequent authorisation is not considered as an appropriate measure in this case as the observed risk is related to the presence of the substance in articles and import of articles is out of the scope of the authorisation process.

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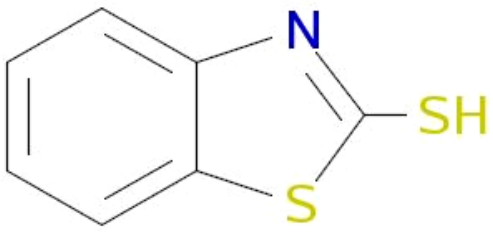
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table 1: Substance identity

Public Name:	Benzothiazole-2-thiol (2-MBT)
EC number:	205-736-8
EC name:	benzothiazole-2-thiol
CAS number (in the EC inventory):	149-30-4
CAS number:	149-30-4
CAS name:	2(3*H*)-Benzothiazolethione
IUPAC name:	1,3-benzothiazole-2-thiol
Index number in Annex VI of the CLP Regulation	613-108-00-3
Molecular formula:	$C_7H_5NS_2$
Molecular weight range:	167.2513 g/mol
Synonyms:	Rubator MBT MBT 2-mercaptobenzothiazole 2(3H)-benzothiazolethione Vulkacit Merkapto

Structural formula:



1.2 Composition of the substance

Name: Benzothiazole-2-thiol (2-MBT)

Description: mono constituent substance, organic

Degree of purity: > 97% (w/w)

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
benzothiazole-2-thiol, EC number: 205-736-8			see confidental annex

Table 3: Impurities

Impurities	Typical concentration	Concentration range	Remarks
see confidental annex			

Table 4: Additives

Additives	Typical concentration	Concentration range	Remarks
not relevant			

1.3 Physico-chemical properties

Table 5: Overview of physicochemical properties

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	*(pale) yellow solid with a disagreeable/pungent odour*	*Handbook data*
Melting/freezing point	*181°C (180-182°C)*	*Handbook data*
Boiling point	*Endothermic effects started at about 140 °C and 250 °C. The second endothermic effect was overlapped by an exothermic reaction;*	*Experimental data according to EU Method A.2;*
	The calculated/estimated boiling point of Benzothiazole-2-thiol is 301.8 ºC.	*Calculated value: EPI-Suite, EPA (USA), Boiling Point Estimations.*
Vapour pressure	*The vapour pressure determined with the gas saturation method was 2.53 *10-6 hPa at 25°C.*	*Experimental data (gas saturation method).*
Surface tension	-	*In accordance with column 2 of REACH Annex VII section 7.6., a study does not need to be conducted because surface activity is not a desired property of the substance and, based on structure, surface activity is not expected.*
Water solubility	*The water solubility of benzothiazole-2-thiol was 118 mg/l at 25°C and pH 7.*	*Experimental data (Campbell Method).*
Partition coefficient n-octanol/water (log value)	*With the shake-flask method a logPow of 2.42 was determined at pH 7;* *The estimated log Pow is 2.86.*	*Experimental data (shake-flask method; equivalent similar to EPA OPPTS 830.7550 (Partition Coefficient, n-octanol / H_2O, Shake Flask Method))* *Calculated value: (EPI-Suite, EPA (USA) / KOWWIN v1.67).*
Granulometry	*- The sample was fractionated by 100 µm sieves and tested by scanning electron microscopy (SEM: Philips XL 30 FEG). The fraction < 100µm was gushed to carbon pads.* *- For the determination of the particle size and aspect ratio, 10 pictures have been taken by scanning electron mikroscopy at a magnification of 1000 times.* *- Mass fraction was calculated for spherical and cubical volume in classes of particle diameters <0.4 µm, 4 -10 µm and 10 -100µm.* *Mass median diameter: 16 µm*	*Experimental data (according to OECD Guideline 110 (Particle Size Distribution / Fibre Length and Diameter Distributions)).*
Stability in organic solvents and	-	*Performing of a test is*

identity of relevant degradation products		*scientifically not necessary. The substance does not contain chemical moieties or reactive groups suggesting instability in organic solvents.*
Dissociation constant	*The pKa of 2-mercaptobenzothiazole at 20 +/- 1°C is 7.03 with a spread of +/- 0.04;*	*Experimental data (Technique UV (235-40)).*
Viscosity	-	*In accordance with section 1 of REACH Annex XI the study on viscosity does not need to be conducted. The substance is solid at environmentally relevant temperature and pressure, and hence no test is necessary.*

2 MANUFACTURE AND USES

2.1 Quantities

Table 6: Aggregated tonnage (per year)

~~1 - 10 t~~	~~10 - 100 t~~	~~100 - 1000 t~~	**1000- 10,000 t**	~~10,000- 50,000 t~~
~~50,000 - 100,000 t~~	~~100,000 - 500,000 t~~	~~500,000 - 1000,000 t~~	~~> 1000,000 t~~	~~Confidential~~

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

not assessed

2.2.2 Use by professional workers

not assessed

2.2.3 Uses by consumers

The substance is mainly used as accelerating agent during the vulcanisation step in the production of rubber.

Consumers use articles made of rubber or containing rubber parts during their subsequent service life. The registrants have addressed this circumstance in an identified use for consumers "Use of tyres and general rubber goods" and/or service life scenarios linked to the following identified uses:

a) "Use of tyres and general rubber goods" further described by article categories AC 1: Vehicles, AC 2: Machinery, mechanical appliances, electrical/electronic articles, AC 3: Electrical batteries and accumulators and AC 10: Rubber articles and the environmental release categories ERC 10a: Wide dispersive outdoor use of long-life articles and materials with low release, ERC 10b: Wide dispersive outdoor use of long-life articles and materials with high or intended release (including abrasive processing) and ERC 11a: Wide dispersive indoor use of long-life articles and materials with low release

b) "Tyre mounting and dismounting and handling of tecnical rubber goods" further described by process category PROC 21: Low energy manipulation of substances bound in materials and/or articles, environmental release category ERC 11a: Wide dispersive indoor use of long-life articles and materials with low release and AC 10: Rubber articles as article category related to subsequent service life.

Literature, data bases and entries of several national product registers researched for this substance evaluation indicate additional applications of the substance in products available to consumers. Data from Switzerland referred to products in the category "paints, laquers and varnishes". The data from the Swedish product register from 2011 (latest data available) lists five consumer products with a

total substance amount of less than 0.1 % of the published aggregated tonnage band (Source: ECHA, 2013).

Such uses have not been identified by the registrants and are outside the scope of their safety assessment (communication to the evaluating member state by the lead-registrant).

2.3 Uses advised against

2.3.1 Uses by workers in industrial settings advised against

not assessed

2.3.2 Use by professional workers advised against

not assessed

2.3.3 Uses by consumers advised against

No uses advised against.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

2-MBT is listed by Index number 613-108-00-3 in Annex VI of the CLP Regulation. The following table shows the CLP classification in Annex VI, Table 3.1 of 2-MBT.

Table 7: Overview on classification and labelling of 2-MBT according to Annex VI, Part 3, table 3.1 (list of harmonised classification and labelling of hazardous (substances) of CLP Regulation

Classification		Labelling			Specific Concen-tration limits, M-Factors	Notes
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Supplementary Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**		
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng		
Aquatic Acute 1	H400					
Aquatic Chronic 1	H410	H410				

Signal Words	Pictograms
Warning	 Exclamation mark  Environment

3.2 Self classification

Self-classification notifications for 2-MBT are available in the C&L Inventory (http://echa.europa.eu/information-on-chemicals/cl-inventory). In the following table an overview (dating of November 2013) of notifications for 2-MBT is given. Three out of 1116 notifiers have notified Carc. 1B.

Table 8: Overview on classification and labelling according to CLP regulation as provided by registrants and notifiers

Classification		Labelling			Specific Concentration limits, M-Factors	Notes	Number of Notifiers
Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**	**Supplementary Hazard Statement Code(s)**	**Pictograms, Signal Word Code(s)**			
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng			382
Aquatic Acute 1	H400	H400					
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng			294
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng			185
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng			148
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng			93
Aquatic Acute 1	H400	H400					
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 Wng			48
Aquatic Acute 1	H400	H400					

Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng			33
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng			19
Aquatic Acute 1	H400	H400					
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng	M=1		5
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng	M=1 M(Chronic) =1		4
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 GHS08 Dgr			2
Carc. 1B	H350	H350					
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng			2
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng	M=1		1
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07			1

Aquatic Chronic 1	H410	H410		GHS09 Wng			
Skin Sens. 1	H317	H317		GHS07 GHS09 Dgr			1
Aquatic Acute 1	H400	H400					
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng	M=10		1
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 Wng	M(Chronic) =1		1
Aquatic Chronic 1	H410	H410					
Skin Sens. 1	H317	H317		GHS07 GHS09 GHS08 Dgr			1
Carc. 1B	H350	H350					
Aquatic Acute 1	H400						
Aquatic Chronic 1	H410	H410					

Number of aggregated notifications: 18

4 ENVIRONMENTAL FATE PROPERTIES

not assessed

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.1.1 Non-human information

Table 9: Overview on basic toxicokinetics according to the registration dossier

Method/ guideline	Route Dose levels, Duration of exposure	Species, Strain, Sex, No/group	Results	Remarks	Reference
Other: toxicokinetic study, GLP study, test protocol reviewed by the EPA	Oral (gavage) dosing with unlabelled MBT (0.510 mg/kg bw) in corn oil for 14d prior to single dose of [^{14}C]-MBT (0.583 mg/kg bw)	Rat (Fisher344) 4/sex/dose	Excretion: 96 h after administration of [^{14}C] MBT >90% of radioactivity were excreted with the urine and 5.22 to 9.99% with the feces No detectable MBT in the urine, but two major metabolites found, the major one being a glucuronide derivate of MBT	Key study by the registrant	El Dareer et al., 1989 TL1 (1987a) unpublished study report
equivalent or similar to OECD Guideline 417 (Toxicokinetics)	Oral (gavage) single dose of [^{14}C]-MBT low dose: 0.592 mg/kg high dose: 55.5 mg/kg	Rat (Fisher344) 4/sex/dose	Urinary excretion of radioactivity from [14C] MBT was rapid and extensive (males low/high and females high dose: >90%; females low dose: 72.1%)	Supporting study by the registrant	El Dareer et al., 1989 TL1 (1986a) unpublished study report

Other: GLP study, comparable to guideline study	Intravenous dosing once with [^{14}C]-MBT 0.602 mg/kg ♂ 0.501 mg/kg ♀	Rat (Fisher344) 4/sex/dose	Excretion: 72 h after administration of [^{14}C] MBT >90% of radioactivity were excreted with the urine and 3.79 to 15.1% with the feces; a small portion (1.52 -1.96%) remained associated with erythrocytes	Supporting study by the registrant	El Dareer et al., 1989 TL1 (1986b) unpublished study report
Method: other: metabolism study	Metabolism of orally administered 2-benzo-thiazoles	Rat (Wistar) male	sulpheneamids partly transformed in the stomach to BTDS and in the liver mainly transformed to MBT and its conjugates	Supporting study by the registrant	Fukuoka, M.; et al., 1987
Other: coverage (dermal) absorption study) occlusive, GLP study, equivalent or similar to OECD Guideline 427 (Skin Absorption: In Vivo Method)	Dermal up to 96 h; single dose of [^{14}C]-MBT 0.0361 mg/ animal on area of 2 cm^2	Rat (Fisher344) 4/sex	Urine was the primary route of excretion (91 to 94% of absorbed radioactivity, feces 4-9%) total percutaneous absorption rate: 16.1 % ♂ 17.5 % ♀	Supporting study by the registrant	El Dareer et al., 1989 TL1 (1987b) unpublished study report
Other: coverage (dermal) absorption study) occlusive, GLP study,	Dermal up to 96 h 0.0361 mg/ animal on area of 5 cm^2	Guinea pig 3 females	Urine was the primary route of excretion (98% of absorbed radioactivity,		El Dareer et al., 1989 TL1 (1987b) unpublished study report

equivalent or similar to OECD Guideline 427 (Skin Absorption: In Vivo Method)			feces 1-2%) total percutaneous absorption rate: 33.4 %		

5.1.2 Human information

No data available from the registration dossiers.

5.1.3 Summary and discussion on toxicokinetics

The toxicokinetic of 2-MBT was evaluated in several studies in rats and guinea pigs (TL1 1986a,b, TL1 1987a,b, El Dareer et al., 1989). Orally administered 2-MBT was readily absorbed and excreted, whereas excretion was primarily in the urine, and small amounts in faeces. Recovery data, after oral or intravenously administered of 2-MBT, did not indicate that appreciable amounts of radioactivity from ^{14}C-labeled MBT were retained in tissues other than blood. Metabolism studies revealed a glucuronide, a glutathione conjugate, the mercapturic acid as well as a sulphate and dibenzothiazyl disulfide as metabolites of 2-MBT in urine. In dermally exposed rats total percutaneous absorption rates of 16.1 % (in males) to 17,5 % (in females) were measured, in female guinea pigs 33.4 %.

5.2 Acute toxicity

5.2.1 Non-human information

5.2.1.1 Acute toxicity: oral

Table 10: Overview of experimental studies on acute toxicity after oral administration according to the registration dossier

Method/ Guideline	**Species, Strain, Sex, No/group**	**Dose levels (mg/kg bw)**	**LD_{50} (mg/kg bw)**	**Remarks**	**Reference**
Oral (gavage) Method: other acute oral	Rat Sprague-	3160 3980	3800 (♂/♀) Clinical signs:	Key study	TL2 (1975) unpublished study report

toxicity study with 14-day post-treatment observation period	Dawley N=5 (mixed males and females)/group	5010 6310 20% test substance suspension (THIOTAX powder) in corn oil	reduced appetite and activity, increased weakness, collapse and death		Randall, D., J.; et al. (1990)[1]
Oral (gavage) Method: other acute oral toxicity study with 14-day post-treatment observation period	Rat Sprague-Dawley N=5 (mixed males and females)/group	2000 2510 3160 3980 MBT (THIOTAX MBT) suspended in corn oil	2830 (♂/♀) Clinical signs: reduced appetite and activity, increased weakness, collapse and death	Supporting study (evaluated as key study by the eMSCA)	TL2 (1974) unpublished study report
Oral (gavage) Method: other acute oral toxicity study with 14-day post-treatment observation period	Rat Wistar males only	Different MBT batches received from different suppliers were tested	9300 (WTR no. 1) 9400 (WTR no. 2) 8600 (WTR no. 3) 8400 (WTR no. 4) 7300 (WTR no. 5)	Supporting study	TL3 (1977)

Further experimental studies on acute toxicity after oral administration are listed in BG Chemie (2000).

5.2.1.2 Acute toxicity: inhalation

No data available from the registration dossiers.

[1] Reference obtained from the CSR, not publicly available

Some experimental studies on acute toxicity after inhalatory administration are listed in BG Chemie (2000).

5.2.1.3 Acute toxicity: dermal

Table 11: Overview of experimental studies on acute toxicity after oral administration according to the registration dossier

Method/ Guideline	**Species, Strain, Sex, No/group**	**Dose levels (mg/kg bw)**	**LD_{50} (mg/kg bw)**	**Remarks**	**Reference**
Dermal (24 h semi occlusive on hair-less skin) Method: other acute dermal toxicity study with 14-day post-treatment observation period	Rabbit New Zealand White N=1-2 (mixed males and females)/group	5010 7940 40 % test substance suspension (THIOTAX powder) in corn oil	> 7940	Key study No mortality occurred Clinical signs: reduced appetite and activity	TL2 (1975) unpublished study report Randall, D., J.; et al. (1990)[1]
Dermal (semi occlusive) Method: other acute dermal toxicity study	Rabbit New Zealand White Male/female	Test substance THIOTAX MBT	> 7940	Supporting study	TL2 (1974) unpublished study report

Further experimental studies on acute toxicity after dermal administration are listed in BG Chemie (2000).

5.2.1.4 Acute toxicity: other routes

No data available from the registration dossiers.

5.2.2 Human information

No data available from the registration dossiers.

5.2.3 Summary and discussion of acute toxicity

Data for evaluating acute oral and acute dermal toxicity of 2-MBT is obtained from animal testing in rats and in rabbits (Randall, D., J.; et al. (1990)[1], TL2 (1974, 1975)). Although none of the

[1] Reference obtained from the CSR, not publicly available

studies was performed according to current test guidelines for acute toxicity testing, the overall available information is sufficient to conclude that the acute toxicity of 2-MBT is low. An **oral LD50 of 2830 mg/kg bw** was determined from a study in male/female rats (Randall, D., J.; et al. (1990)[1], TL2 (1974)) evaluated as key study by the eMSCA and a dermal LD50 of > 7940 mg/kg bw was determined from a study in male/female rats (Randall, D., J.; et al. (1990)[1], TL2 (1975)), both of which can be taken as PoD/dose descriptors for DNEL-derivation.

Based on the results of the available studies, indicating low acute toxicity, 2-MBT does not require classification for acute toxicity according to Regulation (EC) No. 1272/2008 and Directive 67/548/EEC.

5.3 Irritation

5.3.1 Skin

Table 12: Overview of experimental studies on skin irritation according to the registration dossier

Method/ Guideline	**Species, Strain, Sex, No/group**	**Average score** **24, 72 h**	**Results**	**Remarks**	**Reference**
other: skin irritation study, Coverage: semi occlusive (clipped) treatment: 24 h, observation: 7 days mercaptobenzothiazole (MBT), purity: 97.4 %	Rabbit, New Zealand White, 6	Overall irritation score: 0 of max. 8 (mean) no effects at any time point evaluated (readings done at: 4, 24, 48, 72 and 168 h)	not irritating	Key study	TL 2 (1975) unpublished study report Randall, D., J.; et al. (1990)[1]
Method: other skin irritation study, Coverage: semi occlusive (clipped) treatment: 24 h, observation: 7 days Thiotax MBT	Rabbit, New Zealand White, 6	Overall irritation score: 0 of max. 8 (mean) Time point: 24 h, 72 h, no	not irritating	Supporting study	TL2 (1974) unpublished study report

[1] Reference obtained from the CSR, not publicly available

		effects			
Method: other skin irritation study Repeated Insult Patch Test 50 % w/v solution of Thiotax in dimethylphthalate	Human information 50 human volunteers		No visible skin changes after application of the test substance in any of the 50 individuals		TL2 (1976a) unpublished study report

5.3.2 Eye

Table 13: Overview of experimental studies on eye irritation according to the registration dossier

Method/ Guideline	**Species, Strain, Sex, No/group**	**Average score** **24, 48, 72 h**	**Results**	**Remarks**	**Reference**
other: eye irritation study (in vivo) treatment: 24 h, observation: 7 days mercaptobenzothiazole (MBT), purity: 97.4 %	Rabbit, New Zealand White, 6	Overall irritation score: 3.2 of max. 110 (mean) MBT was slightly and transient irritating to the rabbit eye After application: Immediate: discomfort was slight 10 minutes: slight to moderate erythema, moderate to copious discharge 1 hour: slight to moderate erythema, copious discharge (mean score: 8.3/110.0)	not irritating	Key study	TL2 (1975) unpublished study report Randall, D., J.; et al. (1990)[1]

[1] Reference obtained from the CSR, not publicly available

		24 hours: slight to moderate erythema, moderate to copious discharge containing slight whitish exudate (mean score: 8.6/110.0) 48 hours: gradual improvement (mean score: 1.0/110.0) 72 hours: all scored zero fully reversible within 72 h			
Method: other eye irritation study treatment: 24 h, observation: 7 days Thiotax MBT	Rabbit, New Zealand White, 6	Overall irritation score: 1.3 of max. 110 (mean) Thiotax MBT was very slightly and transient irritating to the rabbit eye After application: Immediate: slight discomfort 10 minutes: slight erythema and discharge 1 hour: slight erythema and discharge 24 hours: slight erythema and discharge (mean score 24 h: 4.0/110 48 hours: all scored zero fully reversible within 48 h	not irritating	Supporting study	TL2 (1974) unpublished study report

5.3.3 Respiratory tract

No data available from the registration dossiers.

5.3.4 Summary and discussion of irritation

Data for evaluating skin irritating properties of 2-MBT is available from tests in rabbits and in humans (Randall, D., J.; et al. (1990)[1], TL2 (1974, 1975, 1976)) and for evaluating eye irritation from tests in rabbits. Although no guideline according test had been performed, there is no evidence from the available data for any specific skin or eye irritating properties of 2-MBT. No data are available for respiratory tract irritation.

Based on the results of the available studies, not indicating any specific skin or eye irritating properties, 2-MBT does not require classification as a skin, an eye or a respiratory tract irritant according to Regulation (EC) No. 1272/2008 and Directive 67/548/EEC.

5.4 Corrosivity

No corrosion was seen in the skin/eye irritating tests.

5.5 Sensitisation

5.5.1 Skin

Table 14: Overview of experimental studies on skin sensitisation according to the registration dossier

Method/ Guideline	Species, Strain, Sex, No/group	Number of animals sensitised/total number of animals	Results	Remarks	Reference
GLP and OECD Guideline study: Guinea pig maximisation test according to OECD Guideline 406 Induction: intradermal (5 %) and epicutaneous (25 %) Challenge: epicutaneous, occlusive (12 %) 2-mercapto-benzothiazole, batch no. 01631-077 (supplied by Aldrich Chemie)	guinea pig, other: HSD Poc:DH strain, female treatment group n=10 negative control group n=5	1st reading: 7/10 (test group), 48 h after chall.; dose: 12 % 2nd reading: 6/10 (test group); 72 h after chall.; dose: 12 % 1st reading: 1/5 (neg control); 48 h after chall.;	sensitising	Key study	TL4 (1999) unpublished study report

Vehicle: physiol saline		dose: 0 2nd reading: 0/5 (neg control); 72 h after chall.; dose: 0			
GLP and OECD Guideline study: Guinea pig maximisation test according to OECD Guideline 406 Induction: intradermal (5 %) and epicutaneous (25 %) Challenge: epicutaneous, occlusive (12 %) 2-mercapto-benzothiazole technical grade 98 % Vehicle: physiol saline	guinea pig, other: strain Hsd Poc:DH, female, treatment group n=10	1st reading: 6/10 (test group); 48 h after chall.; dose: 12 % 2nd reading: 6/10 (test group); 72 h after chall.; dose: 12 % 1st reading: 0/5 (neg control); 48 h after chall.; dose: 0 2nd reading: 0/5 (neg control); 72 h after chall.; dose: 0	sensitising	Supporting study	TL4 (1998) unpublished study report
GLP and OECD Guideline study: Guinea pig Buehler test according to OECD Guideline 406 Induction: epicutaneous occlusive (56 %) Challenge: epicutaneous, occlusive (56 & 30 %) 2-mercaptobenzothiazole, purity: 98 % Vehicle: physiol saline	guinea pig, other: strain Bor: DHPW, male treatment group n=12 negative control group n=12	1st reading: 5/12 (test group); 24 h after chall.; dose: 56 % 2nd reading: 3/12 (test group); 48 h after chall.; dose: 56 % 3rd reading: 2/12 (test group); 72 h after chall.;	sensitising	Supporting study	TL4 (1992) unpublished study report

		dose: 56 % 1st reading: 1/12 (test group); 24 h after chall.; dose: 30 % 2nd reading: 0/12 (test group); 48 h after chall.; dose: 30 % 3rd reading: 0/12 (test group); 72 h after chall.; dose: 30 % 7 0/12 (negative control); 24 h after chall.; dose: 0 2nd reading: 0/12 (negative control); 48 h after chall.; dose: 0 3rd reading: 0/12 (negative control); 72 h after chall.; dose: 0			

The above indicated studies were presented as examples for the skin sensitising potential of 2-MBT. A couple of other GMPT and Buehler tests are available in the data base, such as those cited in BG Chemie (2000) and SCCP (2005).

Based on to the results of the above indicated studies and according to the Guidance on the application of the CLP criteria Version 3.0 (Tables 3.4.2./3.4.3) 2-MBT is identified as a **skin sensitiser of moderate potency**.

Table 15: Overview of additional experimental studies on skin sensitisation not considered in the registration dossier

Method/ Guideline	Species, Strain, Sex, No/group	Number of animals sensitised/total number of animals	Results	Remarks	Reference
Mouse local lymph node assay (LLNA) three consecutive concentrations (10, 25 and 50 % in dimethylformamide) of 2-mercapto-benzothiazole from Aldrich	Mouse, CBA/Ca, male /female, treatment groups n=4 Vehicle controls n=4	T/C ratio (ratio of test to control lymphocyte proliferation) of 4.5, 4.6, and 5.5 (at 10, 25 and 50 %)	Sensitising	Classified as positive in comparison to classification according to results from GPMT	Basketer & Scholes, 1992
Mouse local lymph node assay (LLNA) three consecutive concentrations (1, 3 and 10 % in dimethylformamide) of 2-mercapto-benzothiazole from Aldrich	Mouse, CBA/Ca, male /female, treatment groups n=4 Vehicle controls n=4	T/C ratio (ratio of test to control lymphocyte proliferation) of 2.3, 4.4, and 8.6 (at 1, 3 and 10 %)	Sensitising	sensitisation tests performed independently in two laboratories	Basketter et al., 1993
Mouse local lymph node assay (LLNA) w/o modifications (SDS pre-treatment and ex vivo labelling)	Mouse, BALB/c, male or female, treatment groups n=4 Vehicle controls n=4	SI (stimulation index, ratio of test to control lymphocyte incorporation of 3HTdR) of 2.1 – 7.8 Dose-dependent increase in 3HTdR incorporation depending on MBT concentration concentrations SDS pre-treatment (1%) enhancing		MBT across experimental test system classified as of moderate sensitising potential	Basketter et al., 2005

		response			
Mouse local lymph node assay (LLNA) three consecutive concentrations (2.5, 5 and 10 % in acetone:olive oil) of 2-mercapto-benzothiazole from Ohuchi shinko Chem Ind; Tokyo	Mouse, BALB/c, female, treatment groups n=3 Vehicle controls n=4	SI (stimulation index, ratio of test to control lymphocyte incorporation of 3HTdR) of 1.33, 2.23 and 2.51, Dose-dependent increase in 3HTdR incorporation	Sensitising (SI > 2)		Ikarashi et al., 1993 a,b
Mouse local lymph node assay (LLNA) modified (SDS pre-treatment and ex vivo labelling) 5 consecutive concentrations (0.1, 1, 5, 10 and 17,5 % in acetone:olive oil) of 2-mercapto-benzothiazole, 98%, from Aldrich	Mouse, BALB/c, female, treatment groups n=4 Vehicle controls n=4	EC 3 = 9.9 % EC3 (effective concentration inducing a 3-fold increase in proliferation of lymph node cells [SI = 3]	Sensitising potential: moderate	Key study	Van Och et al., 2000; De Jong et al., 2002 a,b
Mouse local lymph node assay (LLNA) modified (biphasic assay [dermal + oral]) dermally 3 consecutive concentrations (3, 10, and 30 % in DMSO), and orally (1, 10, and 1000 mg/kg bw in corn oil) on days 15-17, MBT from Merck KGaA	Mouse, BALB/c, female,		Sensitising potential: mild to moderate		Ahuja et al., 2009

Based on to the results of the study Van Och et al., 2000 and De Jong et al., 2002 a,b and according to the Guidance on the application of the CLP criteria Version 3.0 (Table 3.4.2.) 2-MBT is identified as a skin sensitizer of moderate potency.

Human data on sensitisation

The skin sensitizing potential of 2-MBT was evaluated in a maximization test with human volunteers (Kligman, 1966). Twenty-four human volunteers were patch-tested with 2-MBT. The induction concentration was 25 % 2-MBT, and sodium lauryl sulphate pre-treatment was used.

Provocation was performed with 10% 2-MBT. 9 out of the 24 individuals showed positive response. On a grading scale for potency of 1-5 this rate of sensitisation was graded 3 (moderate).

A study on skin elicitation thresholds was performed on twelve 2-MBT-sensitized test subjects (Emmett et al., 1994). Their allergic sensitivity was confirmed by a diagnostic patch test (2-MBT 1% in petrolatum). Subjects with a positive reaction to the diagnostic 2-MBT test after 4 days were tested with serial dilutions of 2-MBT in petrolatum. An observable reaction was induced in all subjects with concentrations of 0.316% 2-MBT (145 µg 2-MBT/cm^2), whereas the least concentration of 2-MBT applied to any subject that produced an observable reaction was 0.01 % 2-MBT (4.5 µg 2-MBT/cm^2) corresponding to a *total amount* of 2.25 µg 2-MBT. Wide variability occurred with a 100 fold difference among the 12 sensitised subjects. The highest concentration to which no reaction occurred in any individual was 0.0032 % 2-MBT (1.45 µg 2-MBT/cm^2).

The epidemiological data of skin sensitisation of 2-MBT in humans is compiled and reviewed in BG Chemie (2000) and in SCCP (2005) demonstrating that 2-MBT is a relevant allergen for workers mainly in the rubber producing industry as well as in the general population. 2-MBT has been categorised as a category A contact allergen ("significant contact allergen") by the German Federal Institute for Health protection of Consumers and Veterinary Medicine (Kayser and Schlede, 2001).

The contact-allergic skin reaction to 2-MBT 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-MBT, such as gloves, shoes, finger cots, cothing and medical prostheses. Since 2-MBT 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-MBT (Table 11 in BG Chemie, 2000). In patch test series conducted in workers at rubber processing plants, 11 out of 1088 individuals (1%) had positive reactions to 2-MBT (Ziegler & 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-MBT. Patients who had positive reactions to 2-MBT in the standard patch test mostly reacted to other so-called rubber chemicals, such as thiurams, carbamates, phenylenediamines, and as regards latex products, they also reacted to natural latex from the rubber tree. The majority of patients also showed positive reactions to mercapto mix and derivatives of 2-MBT, where tested (cited from BG Chemie, 2000).

It is of interest to note, that according to the German regulation for occupational diseases (BK No. 5101) an occupationally relevant allergy to 2-MBT is scored generally as *mild* and in justified individual cases is scored as *moderate* (Diepgen et al., 2008). In a more recent retrospective analysis (2002-2010) of data (of 93 615 patients) from the Information Network on Departments of Dermatology (IVDK) positive reactions among the patients with occupational dermatitis suspected from glove allergy (including health care workers) to 2-MBT and/or its derivatives were observed at a frequency of 3 %. The reaction frequencies varied with the years, but showed no uniform time trend (Geier et al., 2012).

2-MBT was also addressed in a 5-year (1996-2000) retrospective study of the frequency of sensitization to the 25 allergens of the European standard series (EES) that was conducted in 10 centres in 8 European countries and included a total of 26 210 patients. The percentage of positive reactions to 2-MBT ranged across centres from 0.5 % to 2.0 % with an average percentage of positive reactions of 1 %. The percentage of positive reactions to MBT-mix ranged across centres from 0.3 % to 1.7 % with an average percentage of positive reactions of 1 % (Bruynzeel et al.,

2005). It is of interest to note, that 2-MBT is used in standard series for diagnostic patch testing as either 2-MBT or as Mercapto-mix or both and at different concentrations. The European Environmental and Contact Dermatitis Research Group (EECDRG) recommend to use both, 2-MBT 2% *and* Mercapto-mix 2% (with 0.5 % 2-MBT) (Diepgen et al., 2006).

Toxicological mechanism

Based on in vitro measurements it has been suggested that the SH-group of 2-MBT reacts with the carboxyl group of free amino acids present in the epidermis by oxidation and/or Thioester formation, so that the hapten 2-MBT becomes an allergen (Wang and Tabor, 1988).

5.5.2 Respiratory system

No data available from the registration dossiers.

5.5.3 Summary and discussion on sensitisation

Data for evaluating skin sensitising properties of 2-MBT are available from human evidence and from guideline according animal testing. Based on the results of the animal tests (LLNA, GPMT, Buehler occluded patch test) and according to the Guidance on the application of the CLP criteria (version 3.0) significant sensitising effects were detected in these tests, with 2-MBT assessed to be a skin sensitiser of moderate potency. Available data from earlier tests with human volunteers indicated skin sensitisation from 2-MBT of moderate potency. Further, there is also a large data base on epidemiological data available on patch-test-reactions to 2-MBT, respectively to mercapto-mix or 2-MBT-derivatives or both from different cohorts, indicating positive reactions for 2-MBT at frequencies of about 0.3 to 3 % in patients from dermatology clinics during routinely performed diagnostic patch testing. Recent reviews on the patients in European dermatology clinics/centres indicated positive reactions to 2-MBT at a frequency of 1 %.

No data are available for respiratory tract sensitisation.

Based on the available results from animal testing and from testing in human volunteers it is concluded that 2-MBT is a skin sensitising chemical of moderate potency. Studies (LLNAs) relevant for the evaluation of this endpoint, however not yet considered in the registration dossiers, add up to this WoE evaluation. Although there is considerable information available on the skin sensitising properties from human allergy testing, these data do not afford to propose any sub-categorisation (e.g. Skin Sens. Cat1A or Cat1B). Therefore, the current classification and labelling according to EC No 1272/2008 (CLP) of 2-MBT as Skin Sens. 1 H317 (may cause allergic skin reactions) and according to DSD as R43 (may cause sensitisation by skin contact) is considered appropriate and is confirmed.

Note to the (lead) registrants:

The registration dossier did not recognise the available information on skin sensitisation from tests using the local lymph node assay. This information should be considered for future up-dates of the registration dossier.

5.6 Repeated dose toxicity

5.6.1 Non-human information

5.6.1.1 Repeated dose toxicity: oral

Table 16: Overview of experimental studies on repeated dose toxicity according to the registration dossier

Method/ Guideline	Route of exposure Duration	Species, Strain, Sex, No/group	Dose levels (mg/kg bw/d)	N/LO(A)EL (mg/kg bw/d)	Results Main effects/Target organs	Remarks	Reference
Two generation reproduction study equivalent or similar to OECD Guideline 416*, GLP: yes	Oral (diet)	Rat (SD) Male/female 28/sex/dose	0, 2500, 8750, 15000 ppm	LO(A)EL: 2500 ppm**	LOAEL based on statistically significant body wt gain reduction in F0 males at the lowest dietary concentration tested	key study by registrant	TL1 (1990a) unpublished study Mercieca et al. (1991) abstract
Carcinogenicity study equivalent or similar to OECD TG 451 carcinogenicity study (with exceptions: only two dose levels tested), GLP: yes	Oral (gavage) 103 weeks (5d/week)	Rat (Fisher 344) Male/female 50/sex/dose	Males: 0, 375, 750 Females: 0, 188, 375 (Corn oil)	LO(A)EL/males: 375 LO(A)EL/females: 188	males: ↓ survival rate and lethargic after dosing at 375 and 750 females: lethargic after dosing at 188 and 375 body wts similar or greater than those of vehicle controls	supporting study by registrant	NTP 1988
Method: other subchronic oral toxicity study	Oral (gavage) 13 weeks (5d/week)	Rat (Fisher 344) male/female 10/sex/dose	Males: 0, 188, 375, 750, 1,500 Females: 0, 188, 375, 750, 1,500 (Corn oil)	LO(A)EL males/females: 188	Males: ↓ final body wt at 1,500 ($p<0.05$), ↑ rel. liver organ wt at $\geq$ 188 ($p<0.01$) Females: ↓ final body wt at $\geq$ 750, ($p<0.05$), ↑ rel. liver organ wt at $\geq$ 188 ($p>0.01$) No gross or microscopic effects could be related to chemical administration	supporting study by registrant	NTP 1988
equivalent or similar to OECD	Oral	Mouse (B6C3F1)	Males/ females:	LO(A)EL	Females: ↓ survival rate at	supporting study by	NTP 1988

TG 451 carcinogenicity study	(gavage) 103 weeks (5d/week) (5d/week)	male/female	0, 375, 750	males/ females: 375	750 Males: lower body wts at 375 and 750 m/f: lethargic after dosing at 375 and 750	registrant	
Method: other subchronic oral toxicity study, GLP: no data	Oral (gavage) 13 weeks (5d/week)	Mouse (B6C3F1) male/female 10/sex/dose	Males/ females: 0, 94, 188, 375, 750, 1,500	NO(A)EL males/ females: 188 LO(A)EL males/ females: 375	at 1,500: deaths (5/10 males, 7/10 females), ↑ in rel. liver organ wt (p< 0.10) clonic seizures, lacrimation and salivation at > 750 lethargy and rough coats at 350 and 750 No effects on body wet gain	supporting study by registrant	NTP 1988
Method: other: combined repeated dose and carcinogenicity study	Oral (diet) 20 months (daily)	Mouse (Slc: ddY) male/female 30/sex/dose, control: 60/sex	0, 30, 120, 480, 1920 ppm (males: 3.6, 14.69, 57.90, 289.4 mg/kg bw; females: 0, 3.61, 13.52, 58.87, 247.98 mg/kg bw)	NO(A)EL males/ females: 120 ppm (approx. 14,7 mg/kg bw/d in males and 13,5 mg/kg bw/d in females) LO(A)EL*** males/ females: 480 ppm (approx. 57.9 mg/kg bw/d in males and and 13,5 mg/kg bw/d in females) based on cell infiltration in the interstitium of the kidney in males	↑ mortality rate (m/f) at 1900 ppm, body wt gain reduction (m/f) at 1900 ppm ↓ hematocrit values at 1900 ppm (m at 20 months) and 480 ppm (f at 6 months) no effects on organ wts no effects on biochemical parameters histopath: cell infiltration in the interstitium of kidney at 20 months males: control: 1/14, 30 ppm: 1/6, 120 ppm: 1/7, 480 ppm: 4/6, 1920 ppm: 5/9 females: control: 9/15,	supporting study by registrant	Ogawa et al., 1989

					30 ppm: 2/7, 120 ppm: 5/9, 480 ppm: 3/10, 1920 ppm: 1/7		

*c.f. section 5.9.1.1

**LOAEL of 2500 ppm = approximately 150 – 250 mg/kg bw/d (MAK, 1999)

***LOAEL value suggested by the authors. However, according to MAK (1999) the biological relevance of these findings is questionable because of the low number of animals investigated, the absence of a clear dose response and the lack of a statistic evaluation of the study.

5.6.1.2 Repeated dose toxicity: inhalation

No data available from the registration dossiers.

5.6.1.3 Repeated dose toxicity: dermal

No data available from the registration dossiers.

5.6.1.4 Repeated dose toxicity: other routes

No data available from the registration dossiers.

5.6.2 Human information

No data available from the registration dossiers.

5.6.3 Summary and discussion of repeated dose toxicity

Data for evaluating repeated dose toxicity of 2-MBT is available from several studies in rats and mice with oral administration.

From a two-generation toxicity study in Sprague-Dawley rats (Mercieca et al. (1991), TL1 (1990a)) a LOAEL of 2500 ppm (ca. 150 mg to 250 mg/kg bw/d) was derived. From a two-year carcinogenicity study with Fischer 344 rats a LOAEL of 188 mg/kg bw/d for females and of 375 mg/kg bw/d for males was derived. From a subchronic toxicity study in Fischer 344 rats a LOAEL of 188 mg/kg bw/d was derived for males and females.

From a two-year carcinogenicity study with B6C3F1 mice a LOAEL of 375 mg/kg bw/d was derived for males and females. From a subchronic toxicity study in B6C3F1 mice a NOAEL of 188 mg/kg bw/d was derived for males and females. Thus, from the testing with rats LOAEL values in the range of 150 – 375 mg/kg bw/d were derived. MAK (1999) assumed an overall NOAEL value for rats of 50 mg/kg bw/d, which was taken by the registrant as PoD for DNEL derivation. As a conservative approach the LOAEL value of 188 mg/kg bw/d - as derived from the subchronic and 2-year studies in rats - is proposed to be used as PoD for risk characterization purposes.

No data are available for repeated dose toxicity with the dermal or inhalation route of administration.

Based on the results obtained from repeated dose toxicity testing it is concluded that 2-MBT does not require any classification according to Regulation (EC) No. 1272/2008 and Directive 67/548/EEC.

5.7 Mutagenicity

5.7.1 Non-human information

5.7.1.1 In vitro data

Table 17: Overview of experimental studies on in vitro genotoxicity studies according to the registration dossier

Method/ Guideline	Test system (Organism, strain)	Concentration tested	Results	Remarks (information on cytotoxicity and other)	Reference
Method: other bacterial reverse mutation assay (e.g. ames test), GLP: yes	S. typhimurium, other: TA98, TA100, TA1535, TA1537, TA1538	pre-test: 0, 100, 333, 1000, 3333, 10000 µg/plate main experiment: 0, 3, 10, 30, 100, 300 µg/plate second experiment (+S9 TA 1537, TA98): 0, 100, 250, 300, 450, 600 µg/plate	Negative with and without metabolic activation	Key study by the registrant cytotoxicity: yes (at ≥ 333 µg/plate	TL1 (1984a), unpublished study report
Method: other bacterial reverse mutation assay (e.g. ames test), GLP: no	S. typhimurium, other: TA98, TA100, TA1535, TA1537, TA1538	-S9/+S9: up to 500 ug/plate	Negative with and without metabolic activation	Supporting study by the registrant cytotoxicity: toxic effects indicated at the high dose level, no other specifications	TL2 (1976b) unpublished study report
Method: other bacterial reverse mutation (ames) assay, GLP: yes	S. typhimurium, other: tester strains: TA97, TA98, TA100, TA102	-S9/+S9: up to 5000 ug/plate	Negative with and without metabolic activation	cytotoxicity: yes	TL5 (1984) unpublished study report
Method: other mammalian cell gene mutation assay (HGPRT assay), GLP: yes	Chinese Hamster Ovary cells	dose range finding experiment:- S9/+S9: 0, 0.03, 0.1, 0.33, 1.0, 3.3, 10, 33.33, 100, 333.3, 1000	negative	Supporting study by the registrant Pre-test: cytotoxicity was indicated without S9 at 33.33 (59 % rel. survival) µg/ml and with S9 at	TL1 (1984b) unpublished study report

		µg/ml main experiment: -S9: 0, 1, 5 10, 30, 50 µg/ml; +S9: 0, 10, 25, 75, 150, 300 µg/ml		333.33 µg/ml (17 % rel. survival)	
according to OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test) GLP: yes	mouse lymphoma L5178Y cells	experiment I (-S9/-S9): 0, 10, 20, 30, 50, 75, 100 µg/ml experiment II (-S9/+S9): 0, 20, 30, 40, 50, 60, 70 µg/ml	Negative with and without metabolic activation	Supporting study by the registrant cytotoxicity: yes	TL6 (1997) unpublished study report
Method: other in vitro mammalian chromosome aberration (and endoreduplication) assay, GLP: no data	mammalian cell line, other: CHL cells (female newborn Chinese hamster lung cells)	-S9: 0, 0.2, 0.4 µg/ml +S9: 0, 0.2, 0.4, 0.6 µg/ml	-S9: Frequency of polyploid cells and endoreduplications was 3.6% and 6.2% at 0.2 mg/ml +S9: Frequency of polyploid cells and endoreduplications was 2% and 0.4 % at 0.2 mg/ml inconclusive response at 0.4 mg/ml	Key study by the registrant cytotoxicity: yes chromosome aberration: -S9 negative +S9 inconclusive; increase in polyploid cells and endoreduplications	Matsuoka et al., (2005)
Method: other in vitro mammalian chromosome aberration assay, GLP: no data	Chinese hamster Ovary (CHO) cells	-S9: up to 30.1 µg/ml +S9*: 1st trial: up to 500 µg/ml, 2nd trial: 450 µg/ml	Ambiguous with and without metabolic activation	Supporting study by the registrant cytotoxicity: not determined, cell cycle delay indicated, high toxicity	NTP (1988); Anderson et al., (1990)
Method: other in vitro mammalian sister chromatid exchange assay, GLP: no data	Chinese hamster Ovary (CHO) cells	-S9/+S9: up to 160 ug/ml	Ambiguous with and without metabolic activation	Supporting study by the registrant cytotoxicity: not determined, cell cycle delay indicated, very slight increase, no dose-response, toxicity not determined	NTP (1988); Anderson et al., (1990)

* +S9: 2 h treatment instead of 3 to 6 hours according to OECD TG 473

5.7.1.2 In vivo data

Table 18: Overview of experimental studies on in vivo genotoxicity studies according to the registration dossier

Method/ Guideline	Species, Strain, Sex, No/group	Route & frequency of application	Sampling times	Dose levels	Results	Remarks	Reference
Method: other: in vivo micro-nucleus test, GLP: yes	CD-1 Mouse, male/female, 8 per dose (4 M / 4 F)	Intraperitoneal, single dose or 2 times 300 mg/kg	up to 72 h	300, 600 mg/kg	Negative in both the single and the 2 times treatment group, no statistically significant increase in the number of micronuclei per 1000 polychromatic erythrocytes in the treated versus the control group	Key study by the registrant Toxicity: yes (prostration, hypoactivity, ptosis, tremors and loss of righting reflex after the first dose)	TL1 (1984c) unpublished study report
Method: other: in vivo dominant lethal assay, comparable to guideline study, GLP: yes	Sprague Dawley rat, 28 males per group and 112 females per group	oral: feed, daily, 13 weeks prior to cohabitation, during cohabitation period (serially mated over two weeks) until scheduled sacrifice	Uterine examinations 13 days post-mating	2500, 8750, or 15000 ppm	Negative (significant increases in embryonic death only in females mated with positive control males)	Supporting study by the registrant Toxicity: yes (weight gain reduction at mid and high dose	TL1 (1989) unpublished study report Rodwell, D. J.; et al. (1991)

5.7.2 Human information

No data available from the registration dossiers.

5.7.3 Summary and discussion of mutagenicity

The data for mutagenicity of 2-MBT were obtained from in vitro and in vivo testing. 2-MBT was negative in GLP reverse bacterial mutation assays (Ames test) in bacterial Salmonella thyphimurium strains (TA 98, TA 100, TA 102, TA 1535, TA 1537, 1538) with and without metabolic activation. Gene mutagenic actions of 2-MBT in mammalian Chinese hamster ovary (CHO) cells and in mouse lymphoma L5178Y cells (test in accordance with OECD TG 476) were negative both with and without metabolic activation. An induction of polyploidy cells and endoreduplications was seen in a chromosome aberration assay with CHL cells with and without metabolic activation. No endoreduplications were noted in the solvent control. In limited tests with CHO cells increases in aberrant cells and increases in sister chromatid exchanges were noted. However, the relevance of the results of the tests is questionable, because of presumed high toxicity

and since the results obtained from two independent laboratories were contradictory. The results from the GLP compliant in vivo micronucleus test in mice and from the dominant lethal assay in rats were negative. Therefore, by means of a weight of evidence approach based on the information provided from the registrant it is concluded that 2-MBT is not directly genotoxic.

Based on the results obtained from in vitro and in vivo mutagenicity tests it is concluded that 2-MBT is not genotoxic and does not require any classification according to Regulation (EC) No. 1272/2008 and Directive 67/548/EEC.

5.8 Carcinogenicity

5.8.1 Non-human information

5.8.1.1 Carcinogenicity: oral

Table 19: Overview of experimental studies on carcinogenicity after oral administration according to the registration dossier

Method/ Guideline	**Route of exposure, duration**	**Species, strain, sex, no/group**	**Dose levels (mg/kg bw/d)**	**Results, main effects/ target organs/ tumours**	**NO(A)EL**	**LO(A)EL**	**Remarks**	**Reference**
Equivalent or similar to OECD Guideline 451 (Carcinogenicity Studies) two dose groups evaluated GLP: yes	Oral (gavage) 103 weeks (5 d/week)	Rat (Fisher 344) m/f	m: 0, 375, 750 f: 0, 188, 375 MBT purity: 96.3 to 96.8 % vehicle: corn oil	decreased survival rate (males), animals lethargic and prostration after dosing		LO(A)EL (toxicity): 375 mg/kg bw/d (m) 188 mg/kg bw/d (f)	Key study	NTP(1988)
Equivalent or similar to OECD Guideline 451 (Carcinogenicity Studies) two dose groups evaluated GLP: yes	Oral (gavage) 103 weeks (5 d/ week)	Mouse (B6C3F1) m/f	m/f: 0, 375, 750	decreased survival rate high dose females		LO(A)EL (toxicity): 375 mg/kg bw/d (m/f)	Supporting study	NTP(1988)
Method: carcinogenicity study MTT doses applied,	Oral (diet) 18 months (daily)	Mouse (B6C3F1, B6AKF1) m/f 18/sex/grou	m/f: 100 mg/kg/d for gavage until 4 weeks of	no statistically significant differences between			Supporting study	National Cancer Institute (1968) unpublished study

dosing started at 7 days of age GLP: no data		p	age, continued by 323 ppm in diet	MBT-treated in either strain and the control mice in the incidence of the individual types of tumours				report, Innes, J.R.M. et al. (1969)
Method: Other: combined repeated dose carcinogenicity study GLP: no data	Oral (diet) 20 months (daily)	Mouse /Slc:ddY) m/f	30, 120, 480, and 1920 ppm in diet (males: 3.6, 14.6, 57.9, 289.4 mg/kg bw; females: 0, 3.6, 13.5, 58.9, 248 mg/kg bw	Inhibition of body wt gain at 1920 ppm in males from the initial stage of treatment; cell infiltration in the interstitium of kidney at 1920 and 480 ppm in males at 20 months; no substance-related neoplastic lesions in treated males and females up to the highest dose group evaluated	120 ppm (14.6 mg/kg/d for males; 13.5 for females		Supporting study	Ogawa, Y., et al. (1989)

Part of the following information is based on BG Chemie Nr. 70 (2000)

In a carcinogenicity study, which was conducted as part of an NTP study (NTP, 1988) groups of 50 male and 50 female F344/N rats and of 50 male and 50 female B6C3F1 mice were given 2-MBT 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. Endpoints 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).

Rat

The 2-MBT doses that were selected for the carcinogenicity study proved to be toxic for both dose groups of male rats. A treatment-related, statistically significant ($p < 0.001$) reduction was seen in the survival rates of the male rats at both 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-MBT 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 (up to 11%). 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 in more than 75% of female rats and consisted in nephropathy, 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-MBT. Additionally ulcers and inflammation of the forestomach were prevalent in dosed rats, as were increased incidences of epithelial hyperplasia and hyperkeratosis in male rats, but no neoplasms of the forestomach were observed.

The numbers of animals with neoplastic changes, total numbers of tumours and tumour latent periods are given in the table below.

Table 20: Overview on mortality and tumour incidences of F337N rats after chronic treatment with 2-MBT (NTP, 1988) according to the registration dossier

		Study control (corn oil)	**188 mg/kg bw**	**375 mg/kg bw**	**750 mg/kg bw**	**Historical control (corn oil)**	
						mean	**range**
Mortality	male	8/50	-	28/50	30*/50	-	-
	female	22/50*	19/50*	25/50	-	-	-
Mononuclear cell leukemia	male	7/50 (14%)	-	16/50[a] (32%)	3/50 (6%)	14 ± 8 %	2 - 44% (Haseman 1990)
	female	6/50 (12%)	14/50 (28 %)	9/50 (18 %)	-	19 ± 9 %	4 - 42%
Pancreatic acinar cell adenomas	male	2/50 (4%)	-	13/50 [a, b] 26%)	6/49 (12 %)	6 ± 8 %	0 -28%
	female	-	-	-	-	-	-
Pituitary gland adenomas	male	14/50 (28%)	-	21/50 [a] (42%)	12/48 (25%)	24 ± 8 %	10 -54% (Haseman 1990)
	female	15/50 (31%)	24/50 (48%)	25/50 [a] (50%)	-	37 ± 8 %	18 - 55%

Pituitary gland adenomas or carcinomas (combined)	male	-	-	-	-	26 ± 8%	12 - 44%
	female	16/49 (33%)	24/40 (48%)	25/50 (50%)	-	40 ± 8 %	22 - 61%
Benign pheochromo-cytoma/ adrenal gland	male	18/50 (36 %)	-	25/50 (50%)	22/49 (45%)	23 ± 9 %	4 - 41 %
	female	1/50 (2%)	5/50 (10%)	6/50 [a] (12%)	-	6 ± 4 %	0 -14%
Malignant pheochromoc ytoma/ adrenal gland	male	0/50 (0%)	-	2/50 (4%)	2/49 (4%)	1 ± 1 %	0- 4%
	female	-	-	-	-	0 ± 1 %	0- 2%
Benigne or malignant pheochromo-cytoma/ adrenal gland (combined)	male	18/50 (36%)	-	27/50 [a, b] (54%)	24/49 [a, b] (49%)	24 ± 9 %	4 - 66% (Haseman 1990)
	female	-	-	-	-	6 ± 4%	2 -16%
Preputial gland adenoma	male	0/50 (0%)	-	4/50 (8%)	4/50 (8%)	2 ± 3 %	0 -14%
Preputial gland carcinoma	male	1/50 (2%)	-	2/50 (4%)	1/50 (2%)	2 ± 3 %	0 - 10%
Preputial gland adenomas or carcinoma (combined)	male	1/50 (2%)	-	6/50 [a] (12%)	5/50 [a] (10%)	4 ± 4 %	0 -18%
Total number of animals with benign and/or malignant tumors							
Animals with benign tumors	male	49/50	-	50/50	48/50	-	-
	female	31/50	41/50	36/50	-	-	-
Animals with malignant tumors	male	19/50	-	27/50	15/50	-	-
	female	14/50	21/50	13/50	-	-	-
Animals with benign or malignant tumors (combined)	male	49/50	-	50/50	48/50	-	-
	female	37/50	46/50	40/50	-	-	-

Tumor latent period (weeks)							
benign tumors (wk)	male	90	-	77	56	-	-
	female	62	66	63	-	-	-
malignant tumors (wk)	male	90	-	77	56		
	female	50	56	78	-	-	-
benign or malignant tumors (wk)	male	90	-	77	56	-	-
	female	50	56	63	-	-	-
[a] stat. sign. increased (p<0,05) in comparison to controls, Life Table Analysis [b] stat. sign. increased (p<0,05) in comparison to controls, Incidental Tumor-Test							

* one animal each with dosing accident

Haseman, J. K. et al, Tumor incidences in Fischer 344 rats: NTP historical data
in: Pathology of the Fischer rat, p. 555 -564, Academic Press (1990)

The number of animals that developed tumours was not, or not in a dose-related manner, affected by the administration of 2-MBT. A variety of neoplasms occurred in rats dosed with 2-MBT, however their incidences were not always dose-related. All tumour incidences were within the range of the historical control data (ranges are given in the table) and the changes in tumour incidences were not dose-related, except for dose-related trends observed for benign pituitary gland adenomas in female rats and the adrenal gland phaeochromocytomas. Based on the findings for the latter two tumour sites, the investigators suggested 2-MBT to express some carcinogenic activity in rats at doses increasing mortality. As increased mortality was not dose-related in female rats, the eMSCA questions the relation of tumour growth to mortalities at least for the female sex. The carcinogenic potential based on the pituitary and adrenal gland tumours is considered by the eMSCA equivocal due to the high incidences in the respective internal control groups, which were within the range of historical controls (except the positive trend for benign adrenal tumours in female rats).

Mouse

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 did not show significant non-neoplastic pathological or histopathological lesions.

Incidences of neoplastic changes are given in the table below.

Table 21: Overview on mortality and tumour incidences of B6C3F1 mice after chronic treatment with 2-MBT (NTP, 1988) adapted from BG Chemie (2000)

		Study control (corn oil)	375 mg/kg	750 mg/kg	Historical control (corn oil)	
					mean	range
Mortality	male	11/50	17/50	20/50*	No data	No data
	female	13/50	10/50	28/50*	No data	No data
Hepatocellular adenomas	male	No data	No data	No data	No data	No data
	female	3/50 (6%)	7/49 (14%)	4/50 (8%)	5 ± 4%	0–18%
Hepatocellular carcinomas	male	No data	No data	No data	No data	No data
	female	1/50 (2%)	5/49 (10%)	0/50 (0%)	3 ± 3%	0 – 10%
Hepatocellular adenomas or carcinomas, combined	male	16/49 (33%)	21/50 (28%)	14/50 (28%)	No data	No data
	female	4/50 (8%)	12/49 [a,b] (24%)	4/50 (8%)	8 ± 6%	0 – 28%
Animals with benign tumours	male	20/49	24/50	16/50	No data	No data
	female	25/50	21/49	11/50	No data	No data
Animals with malignant tumours	male	20/49	21/50	14/50	No data	No data
	female	27/50	18/49	9/50	No data	No data
Animals with benign or malignant tumours (combined)	male	31/49	39/50	25/50	No data	No data
	female	38/49	33/49	15/50	No data	No data

* 6 males and 4 females died due to gavage error in week 13

[a] stat. sign. increased ($p<0,05$) in comparison to controls, Life Table Analysis

[b] stat. sign. increased ($p<0,05$) in comparison to controls, Incidental Tumor-Test

The number of animals that developed tumours was not, or not in a dose-related manner, affected by the administration of 2-MBT.

In female mice of the low dose group the incidence of total hepatocellular adenomas or carcinomas (combined) was significantly increased relative to controls, however the finding was not dose-related. Moreover, the incidence was in the range of the historical control data (ranges provided in the table). In the discussion of their results, the investigators noted that possibly the development of

hepatocellular adenomas and carcinomas in the high dose group of female mice could have been masked by reduced survival rate seen in that group, since hepatocellular neoplasms are late-appearing tumour types in mice. Based on the NTP criteria of 1988 on levels of evidence they therefore suggested this finding as *equivocal* evidence for carcinogenic activity. 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. No significant increases in tumour incidences were seen in male mice.

According to the NTP criteria as of 1988 on the levels of evidence of carcinogenic activity the overall results of the study did not provide *clear* evidence of carcinogenic activity, the latter is calling for dose-related increases of malignant neoplasms or of a combination of malignant and benign neoplasms. Based on the tumour incidences with dose-related trends as observed in male and female rats, the authors of the NTP report concluded that there was *some* evidence of carcinogenic activity of 2-MBT, whereas for male and female mice they considered that there was no evidence, respectively equivocal evidence (NTP, 1988). Based on the ambiguous results of this NTP study MAK (1999) assigned 2-MBT to the MAK cancer category 3 ("Substances that cause concern that they could be carcinogenic for man but cannot be assessed conclusively because of lack of data").

In a further long-term dietary carcinogenicity study in Slc:ddY mice, no results were obtained which would have indicated a carcinogenic potential for 2-MBT (Ogawa et al., 1989). The commercial product Nokuseller M (technical grade, no precise details of purity given), was administered to groups of 30 males and 30 females at dietary concentration of 30, 120, 480 and 1920 ppm for 20 months. Based on feed consumption, this corresponded to a daily 2-MBT intake of 3.6, 14.7, 57.9 and 289.4 mg/kg body in males and of 3.6, 13.5, 58.9 and 248 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 volume 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.

In earlier studies, new-born (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-MBT (as the commercial product Captax, purity not specified), formulated in 0.5 % gelatine solution, at the age of 7 to 28 days and subsequently received 323 ppm 2-MBT 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 (National Cancer Institute (1968); Innes et al., 1969).

Cell transformation tests

The cell-transforming potential of 2-MBT 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, concentrations of 10.5, 21, 31.5, 42 and 63 µg 2-MBT/ml (purity not further specified) 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).

5.8.1.2 Carcinogenicity: inhalation

No data available from the registration dossiers.

5.8.1.3 Carcinogenicity: dermal

No data available from the registration dossiers.

5.8.2 Human information

Part of the following information is based on BG Chemie Nr. 70 (2000).

Human information is available from the studies on two occupational cohorts from plants with histories of 2-MBT manufacture and use, one from USA and one from Europe from the UK.

A total of 1059 workers at a rubber chemicals plant in Nitro, West Virginia (USA), were examined in an epidemiological study (Strauss et al., 1993) to find whether they had increased mortality from cancer associated with exposure to 2-MBTand/or derivatives of 2-MBT [sodium 2-mercaptobenzothiazole, N-cyclohexyl-2 benzothiazole sulphenamide, benzothiazyl disulphide, N-tertiary-butyl-2-benzothiazole sulphenamide, 2-(morpholinothio)-benzothiazole, 2-(2,6-dimethyl-morpholinothio)-benzothiazole, 2-(hexamethyleneiminothio)-benzothiazole and 1,3-bis-(2-benzo-thiazolylmercaptomethyl) urea]. There were indications of a possible association between malignant tumours of the urinary bladder and the exposure to 2-MBT and/or its derivatives. However, in addition to 2-MBT 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 produced at the plant between 1935 and 1955. p-Aminobiphenyl (which is classified as Carc. 1A, CLP Regulation) is a compound which the investigators discussed as a possible potent bladder carcinogen at even a relatively 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-MBT was assumed to be equivalent to 2-MBT exposure. A total of 600 workers had exposure to 2-MBT 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-MBT and/or its derivatives was highest during the period between 1943 and 1954, with >2 < 3 mg/m³ on average. During the other years it was ≤1mg/m³ and dropped later on to less than 0.25 mg/m³ after 1970 (see Collins et al., 1999). Because of concern about the potential confounding effect of exposure to p-aminobiphenyl (PAB) with regard to tumour findings, workers with PAB exposure were identified separately and the workers cohort categorised as 2-MBT employees with and without PAB job assignment. Those employees whose work covered all parts of the plant, such as yard labour, maintenance, or general production jobs, were not considered as exposed to PAB. 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 PAB 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-MBT exposure, but mortality from all cancers and mortality from lung, prostate and bladder cancers was raised. The subcohort of 89 workers exposed to 2-MBT *and* PAB 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 511 workers exposed to 2-MBT but not to PAB 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 PAB production was stopped (270 of the 600 workers exposed to 2-MBT), had a lower mortality from all cancers

than the local reference cohort, none of the 8 deaths in this group being attributable to bladder cancer or other cancers (0.03 and 4.26 expected deaths, respectively). With regard to cumulative exposure to 2-MBT, 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-MBT. The investigators critically reviewed 3 deaths from bladder cancer in the sub-cohort of exposed to 2-MBT but not to PAB. As indicated by the cumulative exposure indices, the 3 workers had been in the two highest categories of cumulative exposure to 2-MBT, whereas trend tests did not 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 bladder cancer all occurred at least 20 years after the first exposure, and all 3 workers were employed at the plant even before 1956, which is at a time when PAB was still being used. Although the 3 workers were categorised as not having had exposure to PAB, 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 PAB. Due to this, the investigators recommended further follow-up of the cohort.

As recommended, the cohort from Nitro, West Virginia was followed up (Collins et al., 1999). From the results of the study update, which added 9 years of additional follow-up to the original observation period, it appeared that 2-MBT did not increase the rates of cancers mortalities, including cancer of the prostate and the lung. The study does not allow any definite conclusion with regard to the potential of 2-MBT to cause bladder cancer because of the possibility that there was additional exposure to the potent bladder carcinogen p-aminobiphenyl (PAB), and due to statistical considerations. The standardised mortality ratios (SMRs) calculated for the 600 workers with exposure to 2-MBT 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 analysis in 1993, mortality from 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 sub-cohort of 89 workers with exposure to PAB [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 sub-cohort of 511 workers categorised as not exposed to PAB [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 sub-cohort of 511 workers was categorised as not exposed to PAB was critically reviewed by the investigators of the follow-up study, as a number of the workers must be considered as potentially exposed to PAB (yard labourer, plantwide production worker, maintenance worker). The authors discussed the relevance of the unknown degree of exposure to the known bladder carcinogen p-aminobiphenyl (PAB), which makes it impossible to estimate the risk of bladder cancer due to 2-MBT exposure in this subcohort. Among the 270 workers with exposure to 2-MBT and/or its derivatives but definitely without exposure to PAB as they were not hired until after 1955 – after PAB 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 sub-cohort suggests that 2-MBT lacks urinary bladder carcinogenicity; nevertheless,

based on statistical considerations (number of expected deaths too small in this group), it cannot be stated with certainty that 2-MBT does not contribute to or cause bladder cancer.

In a concomitantly conducted epidemiological study in a total of 2410 workers (2169 males, 250 females) 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-MBT (Sorahan and Pope, 1993). The plant produced 2-MBT, sodium-2-MBT and/or zinc-2-MBT since 1932, whereas production of the 2-MBT derivatives dibenzothiazyl-disulphide, N-oxydiethylene-2-benzothiazolsulphenamide and N-cyclohexyl-2-benzothiazol-sulphenamide began in 1939. Apart from evaluating individual exposures to 2-MBT and/or 2-MBT derivatives (a cohort consisting of 360 workers), also exposures to polymerised 2, 2, 4-trimethyl-1,2-dihydroquinoline (a cohort consisting of 213 workers), to N-cyclohexylthio-phthalamide, phenyl-β-naphthylamine (a cohort consisting of 94 workers) and to aniline or o-toluidine (a cohort consisting of 409 workers) were examined more closely. There was considerable overlap in the membership of the various subcohorts. From the members of the 2-MBT sub-cohort 45 of 360 workers were also exposed to phenyl-β-naphthylamine, 191 of 360 workers also to aniline or o-toluidine and 90 of 360 workers also 2, 2, 4-trimethyl-1,2-dihydroquinoline. Standardised mortality ratios (SMRs) were calculated for the period from 1955 - 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-MBT 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 as presented above (Strauss et al., 1993) which was conducted in parallel at a plant in the USA. Of the total of 360 workers with exposure to 2-MBT and/or its derivatives, 119 died in the period on which the calculations were based, 3 of these died of bladder cancer (1.1 expected deaths). Due to considerable overlap in the membership of the various sub-cohorts, 2 of these 3 bladder cancer death cases had been exposed also to aniline and/or to o-toluidine. In the discussion of their findings, the investigators addressed the fact, that analysis by site of cancer provided little information for confident interpretation due to the small numbers of site-specific deaths.

The cohort of the 2160 male workers was re-examined 10 years later. In this follow-up study (Sorahan et al., 2000) the mortality among the workers was calculated for the 1955–1996 period and the cancer morbidity among the workers was calculated for the 1971–1992 period, in relation to both, the total study cohort (n=2169) as well as the sub-cohorts with exposure to 2-MBT and its derivatives (n=357 workers), aniline (n=385 workers), phenyl-β-naphthylamine (n=94 workers) and/or o-toluidine (n=53 workers). Of the 2160 participants 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 sub-cohorts. For 2-MBT, it was possible to estimate individual cumulative overall exposure (see Sorahan and Pope, 1993), 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 previous study, however, there was no significant increase in the number of deaths from bladder cancer. In the combined sub-cohort of workers with exposure to 2-MBT, 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 individual chemical sub-cohorts, mortality from bladder cancer was significantly increased in the subcohorts with exposure to 2-MBT (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 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-MBT 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-MBT) 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-MBT 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-MBT, 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-MBT 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.

In a recent further follow-up study on this cohort (Sorahan, 2008, 2009) the mortality among the workers was calculated for the 1955–2005 period and the cancer morbidity for the 1971–2005 period, both in relation to the total study cohort but also in relation to the sub-cohorts with exposure to 2-MBT and its derivatives (363 workers), to aniline (442 workers), to phenyl-β-naphthylamine (94 workers) and to o-toluidine (53 workers). Numbers of the membership to the various sub-cohorts differed slightly from those of the former follow-up study, because process descriptions at the plant had been re-visited and re-reviewed for the purpose of this new follow-up. Also, a socalled "combined" subcohort was established (n=611 with exposure to one or more of the chemicals under investigation). Due to the results from the former analyses this recent follow-up study was focused on occupational bladder cancer. Therefore, mortalities from and incidences of bladder cancer were analysed for the overall cohort (n=2160), the combined sub-cohort (n=611 defined as exposure to one or more of the four chemicals under investigation) as well as for the individual chemical sub-cohorts. Two analytical approaches were used, indirect standardisation and Poisson regression. Mortality from all causes combined in the overall cohort was close to expectation (observed 1334, expected1302.3, SMR 102, 95% confidence interval (CI) 97–108) as was mortality from lung cancer (observed 120, expected 131.9, SMR 91, 95% CI 75–109). Mortality from bladder cancer in the overall cohort was non-significantly elevated (observed 22, expected 14.43, SMR 152, 95% CI

96–231). The combined sub-cohort showed an increase in bladder cancer mortality (observed 11, expected 3.96, SMR 278, 95% CI 139-497). Also bladder cancer incidence showed an increase in the combined cohort (observed 18, expected 8.42, SMR 214, 95% CI 127-337). Further, there was a significant positive trend in SMRs for bladder cancer (P<0.05) with period from commencing exposure and no indication of risks decreasing with period from ceasing exposure. In each of the four individual chemical sub-categories the bladder cancer mortality and bladder cancer incidence was also elevated, and a significant positive trend of bladder cancer risk was found with cumulative duration of exposure to *ortho*-toluidine with and without adjustment for the other three chemicals of interest. As the findings for *ortho*-toluidine were consistent with those of three other published studies of chemical production workers that reported highly elevated bladder cancer risks in *ortho*-toluidine-exposed workers (Rubino et al., 1982; Stasik, 1988, Ward et al., 1991) it was concluded that exposure to *ortho*-toluidine was responsible for part of the bladder cancer excess that had occurred in workers at this plant. Concerning the 2-MBT and its derivatives exposed chemical sub-cohort (363 workers), the mortality from all causes was close to expectation, whereas mortality from all neoplasms (observed 76, expected 53.87, SMR 141, 95% CI 111-177), cancer of the large intestine (observed 8, expected 3.45, SMR 232, 95% CI 100-457) and bladder cancer (observed 8, expected 2.14, SMR 374, 95% CI 162-737) were elevated. Non-significant increases in mortality were shown for lung cancer (observed 27, expected 19.51), multiple myeloma (observed 3, expected 0.68), cancer of the kidney (observed 2, expected 0.00) and other cancers of the urinary tract (observed 1, expected 0.06). Based on national cancer incidence rates increased cancer incidences were found for all neoplasms (observed 97, expected 53.87, SMR 148, 95% CI 120-181), bladder cancer (observed 12, expected 4.75, SMR 253, 95% CI 131-441), and mutiple myeloma (observed 4, expected 0.86, SMR 465, 95% CI 127-1191). Non-significant increases in cancer incidence rates were reported for cancers of the large intestine (observed 9, expected 4.97, SMR 181, 95% CI 83-344), cancer of the lung (observed 26, expected 17.08, SMR 152, 95% CI 99-223), cancer of the kidney (observed 3, expected 1.34, SMR 224, 95% CI 46-654) and cancers of the urinary tract (observed 2, expected 0.25, SMR 800, 95% CI 97-2890). Significant positive trends were reported for cumulative duration of exposure to 2-MBT and its derivatives for cancer of the large intestine (p>0.001) and for mutiple myeloma (p>0.01) with and without adjustment for the other three chemicals. The investigators indicated that analysis by site of cancer provides little information for confident interpretation due to the small numbers of site-specific deaths. This applies also to this newly performed follow-up study. In present analysis the authors address that clearly the significant trend shown for multiple myeloma is based on small numbers of deaths (e.g. 2 deaths at none exposure, 2 deaths each at low and intermediate cumulative exposure, 0 deaths at high cumulative exposure). This bearing in mind, also the dose-response relationship for the trend analysis is of highly questionable significance. Concerning the findings on death due to cancer of the large intestine, only one more case added to the cohort in comparison to the former analysis for the 1955-1996 period. Concerning this tumours site the authors had indicated earlier „that there is no convincing evidence that occupational chemical exposures can influence the risks of cancer of the large intestine, and the excess mortality for this disease in the subcohort exposed to 2-MBT may well be a chance finding or represent effects of non-occupational factors. This conclusion applies also to this update and therefore is not interpreted as a serious indication for a specific 2-MBT exposure related tumour site.

5.8.3 Summary and discussion of carcinogenicity

Based on the data available as of 1999 the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (“MAK-Kommission”) assigned 2-MBT 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" (MAK, 1999), due to ambiguous results of the available carcinogenicity study (NTP, 1988). Based on the data available as of 2000 the toxicology advisory council ("Beraterkreis Toxikologie") to the Committee on Hazardous Substances ("Ausschuss für Gefahrstoffe" [AGS]) has not assigned 2-MBT to any of the three legal carcinogenicity categories. Following adoption of the classification proposal in 2001 by the Committee on Hazardous Substances, 2-MBT was not legally classified for mutagenic and/or carcinogenic in the Federal Republic of Germany (BAuA, 2012)

Since the evaluation in 2001 no new data were identified to add to the data base, with the exception of the above indicated further update performed in 2005 on one of the workers cohorts (Sorahan 2008, 2009).

According to the Guidance on the application of the CLP criteria (Version 4.0, November 2013) for regulation (EC) No 1272/2008 classification of substances as a carcinogen is based on consideration of the strength of the evidence of available data for classification with consideration of all other relevant information (weight of evidence) being taken into account. Strength of evidence involves the enumeration of tumours in human and in animal studies and determination of their level of evidence.

Enumeration of tumours in animal studies and determination of their level of evidence:

Tumour types identified in the NTP study (NTP, 1988) and concluded to provide "some evidence of carcinogenic activity" were the following:

♂ F344/N rats: mononuclear cell leukaemia (control: 14%, low: 32%, high: 6%)
pancreatic acinar cell adenomas (control: 4%, low: 26%, high: 12%)
adrenal gland pheochromocytomas (control: 36%, low: 50%, high: 45%)*
preputial gland adenomas or carcinomas (combined) (control: 2%, low: 12%, high: 10%)*

♀ F344/N rats: adrenal gland pheochromocytomas (control: 2%, low: 10%, high: 12%)*
pituitary gland adenomas (control: 31%, low: 48%, high: 50%)*

*= indications for some dose-relatedness derived from positive trends

In addition, tumour types identified and concluded to provide "equivocal evidence of carcinogenic activity" were the following:

♀ B6C3F1 mice: hepatocellular adenomas or carcinomas (combined): control: 8%, low: 24%, high: 8%)

As the incidences of mononuclear cell leukaemia and of pancreatic acinar cell adenomas in male rats and of hepatocellular adenomas and carcinomas in female mice were increased only in the low dose group but not in the higher dose group, there is no reliable evidence of treatment related carcinogenic activity from these tumours sites.

Furthermore, during the NTP study (NTP, 1988) an increase, in particular in spontaneous tumour types was observed in the rats and in female mice. The F344/N rat strain, which was used in this study, is well known for high spontaneous tumour incidences, e.g. for mononuclear cell leukaemia, pituitary adenomas and adrenal pheochromocytomas (NTP, 2007a). The B3C6F1 mouse strain, which was used in this study, is also well known for high spontaneous tumour incidences, e.g. for liver tumours (NTP, 2007b), although it is to be noted that inidences of liver tumours in the internal control group were rather low. In the NTP study (NTP, 1988) the incidences of these particular tumour sites were increased in comparison to the control, however, were all within the contemporary historical incidence range, as were also the incidences of preputial gland adenomas

and carcinomas (combined) in rats of the treated groups (data provided in the table). Therefore, it is concluded that there is no or only very weak evidence for carcinogenic potential of 2-MBT from this study.

With regard to the finding of mononuclear cell leukaemia (MNCL) in the NTP study (NTP, 1988) there is information available, that this tumour type is unique to the rat and is common only for the F 344 strain. MNCL has not been found in other mammalian species and no histopathologically comparable tumour is found in humans. The average historical incidences of MNCL in untreated F-344 rats in NTP bioassays in the period of 1980-1989 amounted to 46.7% in males and to 26.8% in females (NTP, 1994a; cited from Caldwell, 1999). The increased incidence of MNCL following exposure to certain chemical substances is likely a strain-specific effect. The weight of evidence strongly supports MNCL being an F 344 rat strain-specific tumour with questionable biological relevance for humans (Caldwell, 1999).

With regard to the finding of pancreatic acinar cell adenomas in male F 344/N rats in the NTP study (NTP, 1988) there is information available, that occurrence and increased incidences of this tumour type is of equivocal relevance, due to the impact of the corn oil when used as a vehicle. There are studies reporting that male F344/N control rats receiving corn oil by gavage showed a higher incidence of pancreatic acinar cell adenoma than did the corresponding untreated controls. The increased incidences of pancreatic acinar cell adenoma seen in male rats administered corn oil by gavage were associated with elevated body weights observed in these animals relative to untreated controls (Haseman et al., 1985). A specific analysis in 1991 of the NTP database spanning a 4-year time period and including corn oil gavage control groups confirmed the earlier findings that for male F344/N rats corn oil gavage increases the rate of pancreatic acinar cell tumours relative to untreated controls which is probably related to an increase in body weight (Haseman and Rao, 1992).

With regard to the finding of adrenal gland pheochromocytomas in the NTP study (NTP, 1988), for which there is specific propensity to develop in male F 344/N rats, recent data analysis revealed that nephrotoxicity in rats is associated with occurrence of pheochromocytomas (Greim et al., 2009). It hypothesized that nephropathy and calcifications produce a disturbance in renal elimination of calcium and phosphate. Impairment of calcium homeostasis results in proliferation of chromafin cells in the adrenal gland with an increased secretion of catecholamines (Nyska et al., 1999). The nephropathy and endocrine disturbance seems to induce and/or enhances the development of pheochromocytomas. However, up to date, there is no indication that the substances inducing pheochromocytomas in animal experiments also induce corresponding tumours in humans. Chronic progressive nephropathy occurs spontaneously in aging rats with the degree of severity found to be more pronounced in males than in females. High incidences of nephropathy (in all male rats and in more than 75% of the female rats were also reported for the NTP study (NTP, 1988). Nephropathy, characterised by tubular degeneration and regenerations, was observed in all male and in more than 75% of the female rats. The severity of nephropathy was increased in the dosed male rats, notably at doses sufficient to accelerate mortality. A possible association between phaeochromocytomas and nephropathy is also supported by the fact, that when NTP changed the feed (caloric reduction) for male F344 rats, there was a striking decrease in the incidence of chronic nephropathy and simultaneously decreased incidences of phaeochromocytomas and tumours of the pituitary and the preputial glands (Haseman et al., 2003).

It is of interest to note, that the urinary bladder was investigated histopathologically in males and females of both species in the NTP study (NTP, 1988) both in the 13-week and in the two-year study, with no findings of any abnormalities reported. Both of the species used in NTP studies, however, were demonstrated to be sensitive to chemically induced cancer of the urinary bladder

(Huff et al., 1991). Thus, from the NTP study on 2-MBT (NTP, 1988) there is no experimental evidence pointing to any hazard for bladder cancer.

Overall and taking into account, that in the NTP study (NTP, 1988) elevated tumour incidences were found

- for several tumour sites with high spontaneous tumour incidences (mononuclear cell leukaemia, adrenal gland pheochromocytomas, pituitary gland adenomas, liver tumours) in the low dose or both dose groups, however ranging within the contemporary historical control incidences
- for pancreatic cell adenomas (low dose group only), a tumour site with the propensity to develop due to gavage application of corn oil
- for preputial gland adenomas or carcinomas (combined) in the low dose group only ranging within the contemporary historical control incidence

it is concluded that these data do not provide reliable evidence of treatment related carcinogenic activity of 2-MBT.

Therefore, evidence as obtained from the data of animal testing for carcinogenic activity of 2-MBT is not considered appropriate and sufficient to justify a proposal for harmonised classification of 2-MBT for carcinogenicity.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.1.1 Non-human information

Table 22: Overview of experimental studies on fertility according to the registration dossier

Method/ Guideline	Route of exposure, duration	Species, Strain, Sex, No/group	Dose levels	Critical effects parental, offspring (F1, F2)	N/LO(A)EL parental systemic toxicity	N/LO(A)EL reproductive toxicity (fertility)	Remarks	Reference
GLP study, Method: other: equivalent or similar to OECD Guideline 416 with evaluation of oestrus cycle and sperm parameters; test article:	10 weeks before mating, through gestation and lactation until sacrifice for F0 and F1 premating exposure period (males/ females): 10 weeks end of test:		0, 2500, 8750, or 15000 ppm (15000 ppm correspond to ca. 778 to 1328 mg/kg bw/d in F0 males, 779 to 2633 mg/kg bw/d in	LOAEL based on statistically significant body weight gain reduction in F0 males at dietary concen-trations of $\geq$ 2500 ppm and on statistically significant body weight gain reduction in	LOAEL: 2500 ppm	NOAEL: 15000 ppm (equivalent to dietary intake of approxi-mately 745 mg/kg bw/d and more)	Key study by the registrant	TL1 (1990a) unpublished study Mercieca et al. (1991) abstract

MBT lot no.: N8F-228, purity: 98.2 % and 98.5 %	approximately 88 days past weaning		F1 males, 745 to 1760 mg/kg bw/d in F0 females, 980 to 1770 mg/kg bw/d in F1 females)	male and female F0 and F1 animals, increased relative kidney* (F0&F1) and liver (F0) organ weights (due to decreased final body weights) at dietary concentrations of ≥ 8750 ppm				

*Brown pigment was observed in the lumen and epithelial cells of the proximal convoluted tubules with a greater incidence in males than in females. The presence of brown pigment in the lumen suggests a renal route of excretion rather than a toxic effect. Cortical tubular basophilia and alpha 2 µ-globulin inclusions were seen with higher frequency in the males from the treated groups than in the control group.

5.9.1.2 Human information

This information is not available from the registration dossiers.

5.9.2 Developmental toxicity

5.9.2.1 Non-human information

Table 23: Overview of experimental studies on developmental toxicity according to the registration dossier

Method/ Guideline	**Route of exposure, duration**	**Species, Strain, Sex, No/group**	**Dose levels**	**Critical effects 1) dams 2) fetuses**	**L/NO(A)EL maternal toxicity**	**L/NO(AE)L develop-mental toxicity**	**Remarks**	**Reference**
GLP study, comparable to guideline study equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study), MBT purity: 98.1 to 98.5 %	oral: gavage, vehicle: carboxymethyl cellulose, treatment: g.d. 6-18, Caesarean section: g.d. 29	Rabbit New Zealand, 20/group	0, 50, 150, or 300 mg/kg bw/d	1) slightly reduced body weight gain and increased liver weight at 300 mg/kg/d	LOAEL: 300 mg/kg bw/d	NOAEL: 300 mg/kg bw/d	Key study by the registrant	TL1 (1989a) unpublished study report, Rodwell, et al., 1990 (abstract available only)

GLP study, comparable to guideline study equivalent or similar to OECD Guideline 414 (Prenatal Developmental Toxicity Study), MBT purity: 98.1 to 98.5 %	oral: gavage, vehicle: carboxymethyl cellulose, treatment: g.d. 6-15, Caesarean section: g.d. 20	Rat, Sprague Dawley, 26/group	0, 300, 1200, or 1800 mg/kg bw/d	1) salivation, urine staining, dark red material around mouth at 1200 mg/kg/d, reduced body weight at 1800 mg/kg/d	NOAEL: 300 mg/kg bw/d	NOAEL: 1800 mg/kg bw/d	Supporting study by the registrant	TL1 (1989b) unpublished study report, Rodwell, et al., 1990 (abstract available only)

5.9.2.2 Human information

This information is not available from the registration dossiers.

5.9.3 Summary and discussion of reproductive toxicity

Data for evaluating reproductive toxicity of 2-MBT is available from studies in rats and rabbits with oral administration.

From a two-generation toxicity study in Sprague-Dawley rats (Mercieca et al. (1991), TL1 (1990a)) there was no evidence for any adverse effects on reproductive capacity and capability up to and including the highest tested dose. A NOAEL/$_{\text{reproductive toxicity}}$ of 15000 ppm in diet (equivalent to daily intake of 745 – 1328 mg/kg) and a LOAEL/$_{\text{parental systemic toxicity}}$ of 2500 ppm in diet (equivalent to daily intake of 150 mg to 250 mg/kg bw) was derived from this study

From two prenatal developmental toxicity studies with Sprague-Dawley rats and with New Zealand rabbits (Rodwell et al., 1990, TL1 (1989a)) there was no evidence for any prenatal developmental toxicity or any teratogenic effects up to and including the highest tested doses. A NOAEL/$_{\text{prenatal developmental toxicity}}$ of 300 mg/kg bw/d and a LOAEL/ $_{\text{maternal toxicity}}$ of 300 mg/kg bw/d was derived from the study with the non-rodent species which will be taken forward for risk characterisation. For rats there was no evidence for any prenatal developmental toxicity or any teratogenic effects up to and including the highest tested dose of 1800 mg/kg bw/d.

Based on the available data it is concluded that there is no data gap. Based on the results obtained from the available reproductive toxicity and prenatal developmental toxicity testing it is concluded that 2-MBT does not require any classification according to Regulation (EC) No. 1272/2008 and Directive 67/548/EEC

5.10 Endocrine disrupting properties

This information is not available from the registration dossiers.

5.11 Other effects

5.11.1 Non-human information

5.11.1.1 Neurotoxicity

Table 24: Overview of experimental studies on neurotoxicity according to the registration dossier

Method/ guideline	Route of exposure, Duration	Species, Strain, Sex, No/group	Dose levels	NOAEL	LOAEL	Results Main effects	Remarks	Reference
GLP study, equivalent or similar to OECD Guideline 424 (Neurotoxicity Study in Rodents)*	Oral (gavage) Single (acute) exposure	Rat (Sprague Dawley) 12/sex/ dose	0, 500, 1250, 2750 mg/kg bw Vehicle: corn oil	500 mg/kg bw	1250 mg/kg bw	500: increased incidence of salivation in females 1250: females: decreased motor activity, increased incidence of salivation males: decreases in vocalisation	Supporting study by registrant	TL1 (1989c) unpublished report, Bannister et al., 1991
GLP study, equivalent or similar to OECD Guideline 424 (Neurotoxicity Study in Rodents)**	Oral (diet) 91 days	Rat (Sprague Dawley)	0, 5000, 15000, 25000 ppm (ca. 0, 333, 1000, 1667 mg/kg bw/d)	333 mg/kg bw/d	1000 mg/kg bw/d	FOB observational battery: were no pattern of effects observed within or across assessment occasions which was indicative of a treatment-related effect upon behaviour Motor activity: no toxicologically significant differences between treated and control groups for any of the assessment periods. Neuropathological evaluations:	Supporting study by registrant	TL1 (1990b) unpublished report, Bannister et al., 1991

						no treatment-related effects		

*only gross pathological examinations performed, no histopathological examinations
**no ophthalmological examinations performed

5.11.1.2 Immunotoxicity

This information is not available from the registration dossiers.

5.11.1.3 Specific investigations: other studies

This information is not available from the registration dossiers.

5.11.2 Human information

This information is not available from the registration dossiers.

5.11.3 Summary and discussion of specific investigations

not assessed

5.12 Combined effects

This information is not available from the registration dossiers.

5.13 Derivation of DNEL(s) / DMEL(s)

This substance evaluation is targeted to risks for consumers. Therefore, DNELs are derived for the general population only.

Considering the use and exposure scenarios of 2-MBT for consumers as provided in section 9.1.2 of the report (resp. section 10.5.1.2 of the CSR (dating 2013-10-29)) DNELs long-term systemic effects are derived for the oral, dermal and the inhalation routes of exposure for the general population, the latter may be used also for the risk characterisation of short-term/acute systemic effects. The DNELs were calculated according to the REACH Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (Version: 2 December 2010).

Besides the possibility of systemic toxic effects of 2-MBT the substance is also a known skin sensitiser in humans and in experimental animals. Skin sensitisation is generally regarded as a threshold effect; however, the available human and experimental data for 2-MBT are insufficient to derive a threshold and to set a DNEL. Therefore and according to *REACH Guidance on information requirements and chemical safety assessment Part E: Risk Characterisation* the qualitative approach for risk characterisation according to section E.3.4.3 needs to be performed taking into account, that 2-MBT is classified as a Category 1 skin sensitizer.

5.13.1 Overview of typical dose descriptors for all endpoints

Table 25: Overview of studies and dose descriptors per endpoint to be used as PoD for DNEL derivation

Endpoint		**Study**	**Dose descriptor**	**other**
Acute toxicity	Oral	TL2 (1974) unpublished report	LD50: 2830 mg/kg bw	
	Dermal	TL2 (1974, 1975) unpublished reports	LD50: > 7940 mg/kg bw	
	inhalation	No data		
Irritation/Corrosion	Skin			Not irritating
	Eye			Not irritating
	Respiratory tract	No data		
Sensitisation	Skin	WoE from several studies in experimental animals and in humans		Cat1 skin sensitiser
	Respiratory tract	No data		
Repeated dose toxicity: subacute/subchronic/ chronic	Oral	NTP (1988) Fisher 344 rat, 13 weeks	LOAEL: 188 mg/kg bw/d	
	Dermal	No data		
	Inhalation	No data		
Mutagenicity				Data do not support classification as genotoxic
Carcinogenicity	Oral			Data do not support classification as carcinogen
	Dermal	No data		
	Inhalation	No data		
Reproductive toxicity: fertility impairment	Oral	TL1 (1990a) unpublished	NOAEL: 15000 ppm (corresponding to approx. 778-2633	

		study report, Mercieca et al., (1991) abstract	mg/kg bw/d in ♂ and 745-1770 mg/kg bw/d in ♀)	
	Dermal	No data		
	Inhalation	No data		
Reproductive toxicity: pre-natal developmental toxicity	Oral	TL1 (1989a) unpublished study report (rabbit)	NOAEL: 300 mg/kg bw/d	
	Dermal	No data		
	inhalation	No data		

5.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi quantitative descriptor for critical health effects

Considering the use and exposure scenarios of 2-MBT for consumers as provided in section 9.1.2 of the report DNELs long-term systemic effects are derived for the oral, dermal and the inhalation routes of exposure for the general population, the latter may be used also for the risk characterisation of short-term/acute systemic effects. The DNELs were calculated according to the REACH Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (Version: 2.1 November 2012).

DNEL long-term exposure systemic (effects on body and liver organ weight) for oral route

Starting point is a LOAEL of 188 mg/kg bw/d for the endpoint repeated dose toxicity (NTP, 1988; rat, 13 weeks)

AF for correction of LOAEL value to NOAEL value: 3

corrected oral DNEL: 188:3 = **62.7** mg/kg bw/d

data obtained from animal experiment with oral (gavage) administration; in the absence of information → same bioavailability for animals (rats) and humans is assumed, therefore

AF for differences in ABS $_{oral\text{-}rat}$.versus ABS $_{oral\text{-}human}$: 1

data obtained from animal experiment with rat species; therefore

AF for interspecies differences: 4 (for allometric scaling, rat)

2.5 (for remaining differences)

AF for intraspecies differences: 10 (for general population)

data obtained from 13 week/90-day subchronic study, therefore

AF for differences in duration of exposure: 2 (sub-chronic to chronic)

Overall AF: 4 x 2.5 x 10 x 2 = **200**

DNEL: 62.7/200 = **0.31 mg/kg bw/d**

DNEL long-term exposure systemic (effects on body and liver organ weight) for dermal route

Starting point is a LOAEL of 188 mg/kg bw/d for the endpoint repeated dose toxicity (NTP, 1988; rat, 13 weeks)

AF for correction of LOAEL value to NOAEL value: 3

corrected oral DNEL: 188:3 = **62.7** mg/kg bw/d

data obtained from animal experiment with oral (gavage) administration; route-to-route extrapolation from oral to dermal is necessary;

oral bioavailability of 100 % taken into account;

data-based dermal absorption rates taken into account:

17% for rat percutaneous total absorption and 33.4% for guinea pig were determined in an in vivo study (El Dareer et al., 1989); any valid data for human dermal absorption are not available

since rat dermal absorption was unexpectedly low in the above indicated study, and since MW (167,2 g/mol) and Log p_{OW} (2,4) do not account for a default assumption of 10% absorption, the higher dermal absorption rates as determined from guinea pigs are used as here

corrected dermal DNEL: 62.7 mg/kg bw/d x ($ABS_{oral\text{-}rat}/ABS_{derm\text{-}rat}$) x ($ABS_{derm\text{-}rat}$)/$ABS_{derm\text{-}guinea\ pig}$)

corrected dermal DNEL: 62.7 mg/kg bw/d x 3 = **187.7** mg/kg bw/d

data obtained from animal experiment with rat species; therefore

AF for interspecies differences: 4 (for allometric scaling, rat)

2.5 (for remaining differences)

AF for intraspecies differences: 10 (for general population)

data obtained from 13 week/90-day subchronic study, therefore

AF for differences in duration of exposure: 2 (sub-chronic to chronic)

Overall AF: 4 x 2.5 x 10 x 2 = **200**

DNEL: 187.7/200 = **0.94 mg/kg bw/d**

DNEL long-term exposure systemic (effects on body and liver organ weight) for inhalation

Starting point is a LOAEL of 188 mg/kg bw/d for the endpoint repeated dose toxicity (NTP, 1988; rat, 13 weeks)

AF for correction of LOAEL value to NOAEL value: 3

corrected oral DNEL: 188:3 = 62.7 mg/kg bw/d

data obtained from animal experiment with oral (gavage) administration; route-to-route extrapolation from oral to inhalation is necessary;

corrected inhalation DNEL[1]: 62.7 mg/kg bw/d x ($1/sRV_{rat}$) x ($ABS_{oral\text{-}rat}/ABS_{inh\text{-}rat}$) x ($ABS_{inh\text{-}rat}$)/$ABS_{inh\text{-}human}$)

corrected inhalation DNEL: 62.7 mg/kg bw/d x (1/1.15 m^3/kg/d) = **54.5** mg/ m^3

AF for intraspecies differences: 10 (for general population)
2.5 (for remaining differences)

data obtained from 13 week/90-day subchronic study, therefore

AF for differences in duration of exposure: 2 (sub-chronic to chronic)

Overall AF: 2.5 x 10 x 2 = **50**

DNEL: 54.5/50 = **1.09 mg/m^3**

DNEL acute/short-term exposure systemic (effects on body and liver organ weight) for dermal route

The dermal LD50 value of > 7940 mg/kg bw as obtained from a rabbit study is not considered useful for DNEL derivation. According to the REACH Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (Version: 2 December 2010) the acute DNEL also can by default be set as 1-5 times the long-term DNEL. As an appropriate dermal DNEL long-term systemic effect has been derived, the latter is used for establishing a dermal DNEL acute/short-term exposure systemic effects by use of a default AF of 3.

Table 26: Overview on DNELs for the general population to be used for risk characterisation

DNEL/ general population		
long-term, systemic effects	Oral	0.31 mg/kg bw/d
	Dermal	0.94 mg/kg bw/d
	Inhalation	1.09 mg m3
acute/short-term, systemic effects	Dermal	2.82 mg/kg bw/d

These DNELs differ to those used in the registration dossier mainly due to the consideration of different and additional assessment factors (AF).

[1] According to Example B.3 of REACH Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (Version: 2.1 November 2012)

5.14 Conclusions of the human health hazard assessment and related classification and labelling

The available results from animal testing and from testing in human volunteers show that 2-MBT is a skin sensitising chemical of moderate potency. Studies (LLNAs) relevant for the evaluation of this endpoint, however not yet considered in the registration dossiers, add up to this WoE evaluation. Although there is considerable information available on the skin sensitising properties from human allergy testing, these data do not afford to propose any sub-categorisation (e.g. Skin Sens. Cat1A or Cat1B). Therefore, the current classification and labelling according to EC No 1272/2008 (CLP) of 2-MBT as Skin Sens. 1 H317 (may cause allergic skin reactions) and according to DSD as R43 (may cause sensitisation by skin contact) is considered appropriate and is confirmed.

The data available from in vitro and in vivo mutagenicity tests do not support classification of 2-MBT as genotoxic according to Regulation (EC) No. 1272/2008 and Directive 67/548/EEC.

Evidence as obtained from the data of animal testing for carcinogenic activity of 2-MBT is not considered appropriate and sufficient to justify a proposal for harmonised classification of 2-MBT for carcinogenicity.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

not assessed

7 ENVIRONMENTAL HAZARD ASSESSMENT

not assessed

8 PBT AND VPVB ASSESSMENT

not assessed

9 EXPOSURE ASSESSMENT

9.1 Human Health

9.1.1 Exposure assessment for worker

not assessed

9.1.2 Exposure assessment for consumer

9.1.2.1 Overview of uses and exposure scenarios

The substance is mainly used as accelerating agent during the vulcanisation step in the production of rubber. The uses identified by the registrants are set out in section 2.2.3. These uses and the corresponding exposure scenarios take into account that consumers use articles made of rubber or containing rubber parts produced with 2-MBT as a vulcanisation agent during their subsequent service life.

Further information on the exposure assessment for consumers is given in the confidential part.

9.1.2.2 Scope and type of exposure

9.1.2.2.1 Monitoring data

The occurrence of the substance in consumer products has been investigated by a number of migration studies from different rubber articles including soothers. For the majority of samples no migration was detected.

Migration of 2-MBT has been reported for a bottle teat made of natural rubber within a market surveillance performed in the Netherlands in 2001. 0.15 µg of the substance migrated into 40 °C warm water within 24 h after the sample had been cut into stripes and boiled in water for 5 minutes as pre-treatment (Bouma 2002).

In a survey published in 2001 the UK Food Standards Agency reported no detectable migration of 2-MBT from rubber that food and drink come into contact to during their production and storage into 236 samples of different food and drinks. The limits of detection were between 8 µg/kg and 43 µg/kg depending on the type of sample tested (UK Food Standards Agency 2001).

In a series of studies performed in Denmark liberation of 2-MBT from a range of product categories including Toys (e.g. Ballons, Soft Animals and life role play masks), baby articles (e.g. Teething ring), household products, erotic articles and sport articles (e.g. Frogman´s feet) was tested. Migration into a sweat stimulant was observed for a cleaning glove (140-170 µg/dm^2) and an elastic bandage (430-490 µg/dm^2) after incubation of 1 dm^2 at 40°C for 24 hours. The limit of detection was 2 µg/dm^2 and the recovery rate 50-70% (Pors 2003).

In 2008, the German Institute for Risk Assessment (BfR) assessed the health risks of the 2-MBT amounts previously found to migrate from air-matresses in measurements of a federal state surveillance authority. Detected amounts of 2-MBT were 0.49-1.68 mg/dm^2 in a 12 h migration

study with a water based sweat simulant at 40°C and 0.41-1.61 mg/dm^2 in another series with an extraction time of 8 hours. In total 9 samples were tested (BfR 2008).

A method for human biomonitoring of the substance is currently under development.

9.1.2.2.2 Modelled data

Exposure was modelled by the registrants using ECETOC TRA version 3. See confidential part for further information.

9.1.2.2.3 Comparison of monitoring and modelled data

A comparison of the monitoring data presented in section 9.1.2.2.1 with the data modelled by the registrants indicates a lower uptake than the modelled value for the oral and inhalative route, while data for the dermal route is of the same magnitude.

Further information is given in the confidential part.

9.2 Environmental exposure assessment

not assessed

9.3 Combined exposure assessment

not assessed

10 RISK CHARACTERISATION

10.1 Human Health

10.1.1 Workers

not assessed

10.1.2 Consumers

DNEL values for the general population as obtained from the registration dossier are presented in the table below in comparison to the DNEL values for consumers derived by the eMSCA.

Table 27: Overview on the registrants' DNEL values and the DNEL values of the eMSCA

DN(M)ELs for the general population	Route	DNEL / registrant	DNEL / eMSCA
Acute - systemic effects	Dermal (mg/kg bw /day)	20	**2.82**
Acute - systemic effects	Inhalation (mg/m³)	17.6	-
Acute - systemic effects	Oral (mg/kg bw /day)	10	-
Long-term - systemic effects	Dermal (mg/kg bw /day)	2.5	**0.94**
Long-term - systemic effects	Inhalation (mg/m³)	2.2	**1.09**
Long-term - systemic effects	Oral (mg/kg bw /day)	1.25	**0.31**

The differences in DNEL values between the CSR and the eMSCA can be explained by use and consideration of different assessment factors (AF), see section 5.13.2.

Identified uses

The only registered use of 2-MBT relevant for consumers is “Use of tyres and general rubber goods” and its corresponding article service life (see section 2.2.3 Uses by consumers).

Risk characterisation

It is concluded that health risks of consumer exposure to 2-MBT via the oral, dermal and inhalation route with regard to possible systemically toxic effects are sufficiently controlled. See confidential part for further information.

With regard to the skin sensitising property of 2-MBT, for which an appropriate DNEL can not be derived, it is not possible to perform a quantitative risk assessment. As no risk characterisation ratio can be determined, the level of risk for skin sensitisation and/or allergic skin reactions can not be estimated. Therefore, as a conservative approach, and since dermal exposure is likely, any level of dermal exposure is assumed to pose a risk for skin sensitisation/allergic reactions for consumers.

11 OTHER INFORMATION

12 REFERENCES

Author	Year	Title	Publication/source details
Ahuja,V.; Wanner,R.; Platzek,T.; Stahlmann,R.	2009	Appraisal of the sensitising potential of orally and dermally administered Mercaptobenzothiazol by a biphasic protocol of the local lymph node assay	Archives of Toxicology 83 (10), 933-939
Anderson,B.E.; Zeiger,E.; Shelby,M.D.; Resnick,M.A.; Gulati,D.K.; Ivett,J.L.; Loveday,K.S.	1990	Chromosome aberration and sister chromatide exchange test with 42 chemicals	Environmental and Molecular Mutagenesis, 16 (Suppl. 18), 55-137
Bannister,R.	1991	Acute and subchronic neurotoxicity evaluation of 2-mercaptobenzothiazole (MBT) in rats	The Toxicologist 11, 117 (abstract 384)
Basketter,D.A.; Andersen,K.E.; Liden,C.; van Loveren,H.; Boman,A.; Kimber,I.; Alanko,K.; Berggren,E.	2005	Evaluation of the skin sensitizing potency of chemicals by using the existing methods and considerations of relevance for elicitation	Contact Dermatitis 52 (1), 39-43
Basketter,D.A.; Scholes,E.W.	1992	Comparison of the Local Lymph-Node Assay with the Guinea-Pig Maximization Test for the Detection of A Range of Contact Allergens	Food and Chemical Toxicology 30 (1), 65-69
Basketter,D.A.; Selbie,E.; Scholes,E.W.; Lees,D.; Kimber,I.; Botham,P.A.	1993	Results with OECD Recommended Positive Control Sensitizers in the Maximization, Buehler and Local Lymph-Node Assays	Food and Chemical Toxicology 31 (1), 63-67
Berufsgenossenschaft der chemischen Industrie, BG Chemie	2000	Toxikologische Bewertung, 2-Mercaptobenzothialzole, CAS-Nr. 149-30-4	Nr. 170, Ausgabe 11/00
Bouma,K. and Nab,F.M.	2002	TEATS AND SOOTHERS Migration of nitrosamines, nitrosatable substances and 2-mercaptobenzthiazol (MBT) Screening of other migrants Mechanical safety of soothers	INSPECTORATE FOR HEALTH PROTECTION AND VETERINARY PUBLIC HEALTH Report number: NDTOY003/01
Bruynzeel,D.P.; Diepgen,T.L.; Andersen,K.E.; Brandao,F.M.; Bruze,M.; Frosch,P.J.;	2005	Monitoring the European standard series in 10 centres 1996-2000	Contact Dermatitis 53 (3), 146-152

Goossens,A.; Lahti,A.; Mahler,V.; Maibach,H.I.; Menne,T.; Wilkinson,J.D.			
Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA)	2012	Benzothiazol-2-thiol (MBT) / TRGS 905	http://www.baua.de /de/Themen-von-A-Z /Gefahrstoffe/TRGS/pdf/905/ 905-benzothiazol-2-thiol.pdf;jsessionid= 5FC67C5E1A69CEB7E61B 1D707F142133.1_cid380? __blob=publicationFile&v=3
Bundesinstitut fuer Risikobewertung (BfR)	2008	Hilfsstoff zur Herstellung von Gummiluftmatratzen hat allergenes Potenzial	Bundesinstitut fuer Risikobewertung, Opinion No. 033/2008 dated 2008-06-24
Caldwell,D.J.	1999	Review of mononuclear cell leukemia in F-344 rat bioassays and its significance to human cancer risk: A case study using alkyl phthalates	Regulatory Toxicology and Pharmacology 30 (1), 45-53
Collins,J.J.; Strauss,M.E.; Riordan,S.G.	1999	Mortalities of workers at the nitro plant with exposure to 2-mercaptobenzothiazole	Occupational and Environmental Medicine 56 (10), 667-671
De Jong,W.H.	2002	Determination of the sensitising activity of the rubber contact sensitisers TMTD, ZDMC, MBT and DEA in a modified local lymph node assay and the effect of sodium dodecyl sulfate pretreatment on local lymph node responses	Toxicology 176, 123-134
De Jong,W.H.; Van Och,F.M.; Den Hartog Jager,C.F.; Spiekstra,S.W.; Slob,W.; Vandebriel,R.J.; Van,Loveren H.	2002	Ranking of allergenic potency of rubber chemicals in a modified local lymph node assay	Toxicological Science 66 (2), 226-232
Deutsche Forschungsgemeinschaft (DFG) / Maximale Arbeitsplatzkonzentrationen (MAK)	1999	2-mercaptobenzothiazol (2-(3H) –Benzo-thiazolthion)	MAK, 29. Lieferung 1999 (Loseblattsammlung), Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe
Diepgen,T.L.	2008	Beurteilung der Auswirkung von Allergien bei der Minderung der Erwerbsfähigkeit im Rahmen der BK 5101: Thiurame, Mercaptobenzothiazole, Dithiocarbamate, N-Isopropyl-N'-phenyl-p-phenylendiamin	Dermatologie in Beruf und Umwelt 56 (1), 11-24
Diepgen,T.L.; Bruynzeel,D.P.; Andersen,K.E.;	2006	Mercaptobenzothiazole or the mercapto-mix: which should be in the standard series?	Contact Dermatitis 55 (1), 36-38

Brandao,F.M.; Bruze,M.; Goncalo,M.; Goossens,A.; Lahti,A.; Mahler,V.; Menne,T.; White,I.R.; Wilkinson,J.D.			
Dye, C.; Bjerke, A..; Schmidbauer, N.; Manø, S.	2006	Measurement of air pollution in indoor artificial turf halls	Report: NILU OR 03/2006 TA number: TA-2148/2006 ISBN number 82-425-1716-9 Client: Norwegian Pollution Control Authority Executing institution: Norwegian Institute for Air Research (NILU)
el Dareer,S.M.; Kalin,J.R.; Tillery,K.F.; Hill,D.L.; Barnett,J.W.,Jr.	1989	Disposition of 2-meraptobenzothiazole and 2-mercaptobenzothiazole disulfide in rats dosed intravenously, orally, and topically and in guinea pigs dosed topically	Journal of Toxicology and Environmental Health 27 (1), 65-84.
Emmett,E.A.; Risby,T.H.; Taylor,J.; Chen,C.L.; Jiang,L.; Feinman,S.E.	1994	Skin Elicitation Threshold of Ethylbutyl Thiourea and Mercaptobenzothiazole with Relative Leaching from Sensitizing Products	Contact Dermatitis 30 (2), 85-90
European Center for Ecotoxicology and Toxicology of Chemicals	2012	ECETOC TRA version 3: Background and Rationale for the improvements	Technical Report no. 114
European Chemicals Agency (ECHA)	2010	Guidance on information requirements an Chemical Safety Assessment	Chapter R.12: Use descriptor system, Version 2 March 2010
European Chemicals Agency (ECHA)	2013	Information site on registered substances	http://echa.europa.eu/de/information-on-chemicals/registered-substances; last access 26th Novermber 2013; status: last updated on 7th November 2013
Food Standards Agency UK	2001	2-Mercaptobenzothiazole and Benzothiazole from rubber (Number 10/00)	http://www.food.gov.uk/science/research/surveillance/fsis2000/10mbt#.UqmhXKyJzmY; last access 22nd Novermber 2013; status last updated 19th January 2001, Food Survey Information Sheet
Fukuoka,M.; Tanaka,A.	1987	The metabolic orgin of the sufur atom in the sulfhydryl group of 2-thiobenzothiazole metabolites derived from benzothiazyl sulfenamide in the rat	Archives of Toxicology 61 (2), 158-160
Geier,J.; Lessmann,H.; Mahler,V.;	2012	Occupational contact allergy caused by rubber gloves - nothing has changed	Contact Dermatitis 67 (3), 149-156

Pohrt,U.; Uter,W.; Schnuch,A.			
Greim,H.; Hartwig,A.; Reuter,U.; Richter-Reichhelm,H.B.; Thielmann,H.W.	2009	Chemically induced pheochromocytomas in rats: mechanism and relevance for human risk assessment	Critical Reviews in Toxicology 39 (8), 695-718
Haseman,J.K. et al	1990	Tumor incidences in Fischer 344 rats: NTP historical data	in: Pathology of the Fischer rat, p. 555 -564, Academic Press (1990)
Haseman,J.K.; Huff,J.E.; Rao,G.N.; Arnold,J.E.; Boorman,G.A.; Mcconnell,E.E.	1985	Neoplasms Observed in Untreated and Corn-Oil Gavage Control-Groups of F344/N Rats and (C57Bl/6N X C3H/Hen)F1 (B6C3F1) Mice	Journal of the National Cancer Institute 75 (5), 975-984
Haseman,J.K.; Ney,E.; Nyska,A.; Rao,G.N.	2003	Effect of diet and animal care/housing protocols on body weight, survival, tumor incidences, and nephropathy severity of F344 rats in chronic studies	Toxicologic Pathology 31 (6), 674-681
Haseman,J.K.; Rao,G.N.	1992	Effects of Corn Oil, Time-Related Changes, and Inter-Laboratory Variability on Tumor Occurrence in Control Fischer 344 (F344/N) Rats	Toxicologic Pathology 20 (1), 52-60
Haseman,J.K.; Young,E.; Eustis,S.L.; Hailey,J.R.	1997	Body Weight-Tumor Incidence Correlations in Long-Term Rodent Carcinogenicity Studies	Toxicologic Pathology 25 (3), 256-263
Huff,J.; Cirvello,J.; Haseman,J.; Bucher,J.	1991	Chemicals Associated with Site-Specific Neoplasia in 1394 Long-Term Carcinogenesis Experiments in Laboratory Rodents	Environmental health perspectives 93, 247-270
Ikarashi,Y.; Tsuchiya,T.; Nakamura,A.	1993	A Sensitive Mouse Lymph-Node Assay with 2 Application Phases for Detection of Contact Allergens	Archives of Toxicology 67 (9), 629-636
Ikarashi,Y.; Tsuchiya,T.; Nakamura,A.	1993	Evaluation of Contact Sensitivity of Rubber Chemicals Using the Murine Local Lymph-Node Assay	Contact Dermatitis 28 (2), 77-80
Innes,J.R.M.; Ulland,B.M.; Valerio,M.G.; PETRUCEL.L; Fishbein,L.; Hart,E.R.; Pallotta,A.J.; Bates,R.R.;	1969	Bioassay of pesticides and industrial chemicals for tumorigenicity in mice: a preliminary note	Journal of the National Cancer Institute 42 (6), 1101-1114

Falk,H.L.; Gart,J.J.; Klein,M.; Mitchell,I.; Peters,J.			
Ishmael,J.; Dugard,P.H.	2006	A review of perchloroethylene and rat mononuclear cell leukemia	Regulatory Toxicology and Pharmacology 45 (2), 178-184
Kayser,D.; Schlede,E.	2001	Chemikalien und Kontaktallergie. Eine bewertende Zusammenstellung (Loseblattsammlung)	Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (heute: Bundesinstitut für Risikobewertung BfR), Verlag Urban & Vogel, ISBN 3-86094-163-1
Kligman,A.M.	1966	The identification of contact allergens by human assay	The Journal of Investigative Dermatology 47 (5), 393-409
Litton Bionetics, Inc.	1982	Evaluation of MBT in the in vitro transformation of BALB/3T3 cells assay	unveröffenlichter Bericht, LBI Project No. 20992 (1982), im Auftrag der Goodyear Tire & Rubber Co.
Maryadele J.O, Hechkelman PE, Kock CH, Roman KJ	2006	The Merck Index. An Encyclopedia of Chemicals, Drugs and Biologicals.	The Merck Index. An Encyclopedia of Chemicals, Drugs and Biologicals. Merck & Co. Inc, Whitehouse Station, NJ, USA 2006, page 1014
Matsuoka,A.; Isama,K.; Tsuchiya,T.	2005	In vitro induction of polyploidy and chromatid exchanges by culture medium extracts of natural rubbers compounded with 2-mrcaptobenzothiazole as a positve control candidate for genotoxicity tests	Journal of Biomedical Materials Research Part A, 75A (2), 439-444
Matthews,E.J.; Spalding,J.W.; Tennant,R.W.	1993	Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in Salmonella and carcinogenicity in rodent bioassays	Environmental Health Perspectives 101 (Suppl. 2), 347-482
Mercieca,M.	1991	Mercaptobenzothiazole (MBT): A two-generation study using Sprague-Dawley rats	The Toxicologist 11 (2), 112 (abstract)
National Cancer Institute (NCI)	1968	Evaluation of carcinogenic, teratogenic, and mutagenic activities of selected pesticides and industrial chemicals. Volume I. Carcinogenic study	Data Bionetics Research Laboratories, Maryland, USA, National Technical Information Service PB-223 159
National Institute for Occupational Safety and Health (NIOSH)	2004	International Pocket Guide to Chemical Hazards: 2-mercaptobenzothiazole	http://www.cdc.gov/niosh/ipcsneng/neng1183.html
National Toxicology Program (NTP)	1988	Toxicology and carcinogenesis studies of 2-mercaptobenzo-thiazole, CAS no. 149-30-4, in F334/N rats and B6C3F1 mice, appendix E, genetic toxicology of 2-mercaptobenzothiazole	National Toxicology program, NTP TR 332, NIH Publication No. 88-2588. Testing laboratory: Physiological Research Laboratories (Minneapolis, Minnesota)
National Toxicology	1994	Comparative toxicology studies in corn oil, safflower oil, and tricaprylin in male F344/N	NIH Publication No. 94-3157,

Program (NTP)		rats as vehicle for gavage	NTP TR 426 (1994)
National Toxicology Program (NTP)	1994	Toxicology Data Management System Historical Control Tumor Incidence Report	Analytical Sciences, Research Triangle Park, NC
National Toxicology Program (NTP)	2007	Historical Controls Report All Routes And Vehicles. MICE, October 2007	http://ntp.niehs.nih.gov/?objectid=92E705C7-F1F6-975E-72D23026B1645EB9
National Toxicology Program (NTP)	2007	Historical Controls Report All Routes And Vehicles. RATS, October 2007	http://ntp.niehs.nih.gov/?objectid=92E705C7-F1F6-975E-72D23026B1645EB9
Nyska,A.; Haseman,J.K.; Hailey,J.R.; Smetana,S.; Maronpot,R.R.	1999	The association between severe nephropathy and pheochromocytoma in the male F344 rat - The National Toxicology Program experience	Toxicologic Pathology 27 (4), 456-462
OECD Environmental Health and Safety Publications	2004	Emission Scenario Document on Additives in Rubber Industry	Series on Emmission Scenario Documents No. 6; ENV/JM/MONO(2004)11; http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono%282004%2911&doclanguage=en
Ogawa,Y.; Kamata,E.; Suzuki,S.; Kobayashi,K.; Naito,K.; Kaneko,T.; Kurokawa,Y.; Tobe,M.	1989	[Toxicity of 2-mercaptobenzothiazole in mice]	Eisei Shikenjo Hokoku (jap.) = Bulletin of the National Institute of Hygienic Sciences, Issue 107, 44-50 [Article in Japanese]
Pors, J.; Fuhlendorff, R.	2003	Liberation of MBT in natural rubber	Survey of Chemical Substances in Consumer Products Survey No 22, 2003
Randall,D.J.; Bannister,R.M.	1990	Acute toxicologic evaluation of mercaptobenzothiazole	Journal of American College of Toxicology, part B, vol.1, 62[1]
Rodwell,D.E.	1990	Developmental toxicity study of 2-mercapto-benzothiazole (MBT) in two species	Teratology p. 587 (abstract)
Rodwell,D.E.; Mercieca,M; Barnett,J.W.,Jr.; Murphy,S.J.	1991	Mercaptobenzothiazole (MBT): A dominant lethal evaluation	The Toxicologist 11 (2), 247 (abstract)
Rubino,G.F., Scansetti,G., Piolatto,G., Pira,E.	1982	The carcinogenic effect of aromatic amines: an epidemiological study of the role of o-toluidine and 4,4'-methylene bis(2-methylaniline) in inducing bladder cancer in man	Environmental Research 27 (2), 241–254
Scientific	2005	Scientific Committee on Consumer	European Commission, Health &

[1] Reference obtained from the CSR, not publicly available

Committee on Consumer Products (SCCP)		Products, Opinion on 2-mercaptobenzothiazole (MBT) (Sensitisation only)	Consumer Protection Directorate-General
Sorahan,T.	2008	Bladder cancer risks in workers manufacturing chemicals for rubber industry	Occupational Medicine -Oxford 58 (7), 496-501
Sorahan,T.	2009	Cancer risk in chemical production workers exposed to 2-mercaptobenzothiazole	Occupational and environmental medicine 66 (4), 269-273
Sorahan,T.; Hamilton,L.; Jackson,J.R.	2000	A further cohort study of workers employed at a factory manufacturing chemicals for the rubber industry, with special reference to the chemicals 2-mercaptobenzothiazole (MBT), aniline, phenyl-beta-naphthylamine and o-toluidine	Occupational and environmental medicine 57 (2), 106-115
Sorahan,T.; Pope,D.	1993	Mortality study of workers employed at a plant manufacturing chemiclas for the rubber industry: 1955-86	British Journal of Industrial Medicine 50 (11), 998-1002
Stasik,M.J.	1988	Carcinomas of the urinary bladder in a 4-chloro-o-toluidine cohort	International Archives of Occupational and Environmental Health 60 (1), 21–24
Strauss,M.E.; Barrick,E.D.; Bannister,R.M.	1993	Mortality experience of employees exposed to 2-mercaptobenzothiazole at a chemical plant in Nitro, West Virginia	British Journal of Industrial Medicine 50 (10), 888-893
TL1	1984a	Ames Salmonella/microsome plate test, mercaptobenzothiazole	Unpublished study report
TL1	1984b	CHO/HGPRT mammalian cell forward gene mutation assay, mercaptobenzothiazole	Unpublished study report
TL1	1984c	Genetic Toxicology, micronucleus test (MNT), mercaptobenzothiazole	Unpublished study report
TL1	1986a	Disposition of 2-mercaptobenzothiazole-ring-UL-14C and 2-mercaptobenzothiazole disulfide-ring-UL-14C in Fischer 344 male and female rats dosed orally, final report	Unpublished study report
TL1	1986b	Dispostion of 2-mercaptobenzothiazole-ring-UL-14C and 2-mercaptobenzothiazole disulfide-ring-UL-14C in Fischer 344 male and female rats dosed intravenously	Unpublished study report
TL1	1987a	Disposition of 2-mercaptobenzothiazole-ring-UL-14C in Fischer 344 male and female rats dosed orally after repeated dosing with the unlabbeled compound, final report	Unpublished study report
TL1	1987b	Absorption and disposition of 2-mercaptobenzothiazole-ring-UL-14C and 2-mercaptobenzothiazole disulfide-ring-UL-14C in Fischer 344 male and female rats and female guinea pigs dosed topically, final report	Unpublished study report

TL1	1989	A dominant lethal study in rats with MBT, final report	Unpublished study report
TL1	1989a	Teratology study in rabbits with MBT	Unpublished study report
TL1	1989b	Teratology study in rats with MBT	Unpublished study report
TL1	1989c	An acute study of the potential neurotoxic effects of 2-mercaptobenzothiazole in rats	Unpublished study report
TL1	1990a	Two generation reproduction study in rats with MBT	Unpublished study report
TL1	1990b	A 3-month study of the potential effects of orally administered 2-mercaptobenzothiazole on behavior and neuromorphology in rats	Unpublished study report
TL2	1974	Toxicologic investigation of: Thiotax MBT	Unpublished study report
TL2	1975	Toxicologic investigation of Thiotax powder	Unpublished study report
TL2	1976a	Evaluation of potentail hazards by dermal contact	Unpublished study report
TL2	1976b	Mutagenicity evaluation of BIO-76-177 CP1975 Thiotax, final report	Unpublished study report
TL3	1977	Determination of the acute oral toxicity of five samples of mercaptobenzthiazole in rats	Unpublished study report
TL4	1992	Überprüfung der im Fachbereich Toxikologie der Bayer AG angewandten Methodik des Buehler-Tests am Meerschweinchenstamm DHPW unter Verwendung von 2-Mercaptobenzothiazole	Unpublished Study report
TL4	1998	Validation of the Magnusson-KligmanMaximization Test method used by the Fachbereich Toxikologie, Bayer AG performed in guinea pigs of the strain Hsd Poc: DH with 2-mercaptobenzothiazole.	Unpublished study report
TL4	1999	Validation of the Magnusson-Kligman Maximization Test Method used by the Fachbereich Toxikologie, Bayer AG, performed in guinea pigs of the strain Hsd Poc: DH with 2-mercaptobenzothiazole	Unpublished study report
TL5	1984	Ames Salmonella / microsome, compound name: MBT	Unpublished study report
TL6	1997	2-mercapto-benzothiazole: L5178Y TK +/- mouse lymphoma mutation assay	Unpublished study report
van Och,F.M.M.	2000	A quantitative method for assessing the sensitizing potency of low molecular weight chemicals using a local lymph node assay: employment of a regression method that includes determination of the uncertainty margins	Toxicology 146 (1), 49-59
Wang,X.S.; Tabor,M.W.	1988	Studies of the Reactivity of Morpholine, 2-Mercaptobenzothiazole and 2 of Their Derivatives with Selected Amino-Acids	Contact Dermatitis 19 (1), 16-21
Ward,E.; Carpenter,A.; Markowitz,S.;	1991	Excess number of bladder cancers in workers exposed to ortho-toluidine and	Journal of the National Cancer Institute

Roberts,D.; Halperin,W.		aniline	83 (7), 501-506
Wu, F.-L.; Hussein, W.M.; Ross, B.P.; McGeary, R.P.	2012	2-Mercaptobenzothiazole and its Derivates: Syntheses, Reactions and Applications	Current Organic Chemistray, Vol. 16, Pages 1555-1580
Ziegler,V.; Süss,E.	1974/75	[The allergenic effect of rubber accelerators tetramethyl thiuram disulfide (TMTD) and mercaptobenzothiazole (MBT)] [Article in German]	Allergie und Immunologie (Leipz.) 20-21 (3), 281-285

13 ABBREVIATIONS

Table 28: List of abbreviations

ABS	Absorption
AC	Article category
AF	Assessment Factor
Bw	Body weight
CSR	Chemical Safety Report
DNEL	Derived No-effect level
eMSCA	Evaluating Member state competent authority
ERC	Environmental release category
ES	Exposure Scenario
HBM	Human Biomonitoring
IU	Identified use
LC50	Median lethal concentration. The concentration causing 50% lethality
LD50	Median lethal dose. The dose causing 50% lethality
LOAEL	Lowest observed effect level
2-MBT	2-Mercaptobenzothiazole
NTP	National Toxicology Program
PC	Product category
phr	Parts per hundred rubber
PoD	Point of Departure
PROC	Process category
RCR	Risk Characterisation Ratio
sRV	Standard respiratory volume
SU	Sector of end use