

N-Cyclohexylbenzothiazol-2-sulphenamide

CAS No: 95-33-0

EINECS No: 202-411-2

SUMMARY RISK ASSESSMENT REPORT

Final report, May 2008

Germany

FINAL APPROVED VERSION

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance N-Cyclohexylbenzothiazol-2-sulphenamide that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau¹. The Final RAR should be used for citation purposes rather than this present Summary Report.

¹ European Chemicals Bureau – Existing Chemicals – <http://ecb.jrc.it>

CONTENTS

1	GENERAL SUBSTANCE INFORMATION	3
1.1	IDENTIFICATION OF THE SUBSTANCE.....	3
1.2	PURITY/IMPURITIES, ADDITIVES	3
1.3	PHYSICO-CHEMICAL PROPERTIES.....	3
1.4	CLASSIFICATION	4
2	GENERAL INFORMATION ON EXPOSURE	6
3	ENVIRONMENT.....	7
3.1	ENVIRONMENTAL EXPOSURE	7
3.2	EFFECTS ASSESSMENT	10
3.3	RISK CHARACTERISATION	13
4	HUMAN HEALTH.....	17
4.1	HUMAN HEALTH (TOXICITY)	17
4.1.1	Exposure assessment	17
4.1.2	Effects assessment	19
4.1.3	Risk characterisation.....	24
4.2	HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)	32
5	RESULTS.....	33
5.1	ENVIRONMENT	33
5.2	HUMAN HEALTH	34
5.2.1	Human health (toxicity).....	34

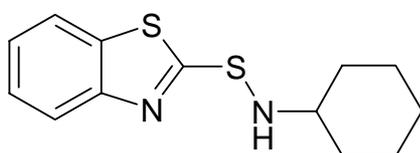
TABLES

Table 1.1	Summary of physico-chemical properties.....	4
Table 3.1	Relevant degradation products of CBS and their selected environmental properties.....	8
Table 3.2	Aquatic PNECs of CBS and its degradation products.....	10
Table 3.3	PNEC _{soil} of CBS degradation products	12
Table 3.4	Risk characterisation ratios of CBS for the production sites.....	14
Table 3.5	Risk characterisation ratios of degradation products.....	14
Table 3.6	Risk characterization of CBS breakdown products for use in tires.....	15
Table 3.7	Risk characterisation of CBS breakdown products for road border soil based on measured data ..	16
Table 4.1.1	Summary of exposure data.....	18
Table 4.1.3.A	Occupational exposure levels and internal body burden (CBS).....	25
Table 4.1.3.B	Summary on occupational risk assessment.....	31

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number:	95-33-0
EINECS Number:	202-411-2
IUPAC Name:	N-Cyclohexylbenzothiazol-2-sulphenamide
Synonyms:	2-Benzothiazolesulfenamide, N-cyclohexyl- Benzothiazyl-2-cyclohexylsulfenamide 2-(Cylcohexylaminothio)benzothiazole CBS N-cylcohexyl-2-benzothiazolesulfenamide
Molecular weight:	264.4 g/mol
Molecular formula:	C ₁₃ H ₁₆ N ₂ S ₂
Structural formula:	



1.2 PURITY/IMPURITIES, ADDITIVES

Purity: $\geq 96\%$

Impurities:

Disulphides and sulfinic acid derivatives of mercaptobenzothiazole, dimercaptobenzothiazoles and methylmercaptobenzothiazoles < 3%

Di(benzothiazol-2-yl)disulphide $\leq 0.5\%$

Cyclohexylamine $\leq 0.5\%$

Water $\leq 0.3\%$

1.3 PHYSICO-CHEMICAL PROPERTIES

N-cylcohexylbenzothiazole-2-sulfenamide (CBS) is a grey or yellow powder with a slight odour. Data on the physical and chemical properties are given in the following table:

Table 1.1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	solid	
Melting point	97.5-105 °C	Monsanto (1968) Bayer (1969)
Boiling point	Decomposition starts at 145 °C	Bayer (1997)
Relative density	1.286 at 20 °C to water at 4 °C	Bayer (1997)
Vapour pressure	1.5x10 ⁻⁸ hPa at 20 °C ¹⁾	Bayer (1988)
Water solubility	0.32 mg/l at 21 °C (pH 7) ²⁾	Monsanto (1980a)
Partition coefficient n-octanol/water (log value)	logPow 4.93 ³⁾	Monsanto (1980a)
Granulometry		
Conversion factors		
Flash point	not applicable (solid)	
Autoflammability	no selfignition until the melting point	Bayer (1997)
Flammability	not highly flammable	Bayer (1997)
Explosive properties	not explosive	due to structural reasons
Oxidizing properties	no oxidizing properties	due to structural reasons
Viscosity		
Henry's constant		
Surface tension	no data ⁴⁾	

¹⁾ The vapour pressure was determined using the gas saturation method and confirmed by entries in safety data sheets of various companies²⁾ not relevant for the risk assessment

²⁾ The water solubility was determined with the column elution method. Buffer solutions were used. The water solubility at pH 5 was 0.24 mg/l and 0.48 mg/l at pH 9 (21 °C).

³⁾ The shaking flask method was used for the determination of the partition coefficient n-octanol/water. The calculation with SRC-LOGKOW for Microsoft Windows resulted in a logPow of 3.47. For the risk assessment the experimental value is preferred.

⁴⁾ not relevant for the risk assessment

1.4 CLASSIFICATION

Classification (25. ATP): R43 May cause sensitization by skin contact
 R50/53 Very toxic to aquatic organisms, may cause
 long-term adverse effects in the aquatic
 environment

Labelling:

Xi
N

Sensitizing
Dangerous for the environment

2

GENERAL INFORMATION ON EXPOSURE

Production

In the European Union (EU-15), CBS is produced at three sites. One additional company is solely importing. According to the data supplied by these four companies, 16 101 t/a are produced, 431 t/a are imported and 10 524 t/a exported outside of the EU. Thus 6 008 t/a of this substance flow are consumed within Europe. In addition, HPV-scale import not subject to the Regulation 93/793/EEC occurs in the EU-15. A total market volume of 20 000 t/a is assumed in this assessment.

CBS and other benzothiazole sulphenamides are obtained by oxidation of a mixture of MBT or NaMBT and cyclohexylamine or other amines.

Uses

CBS is exclusively used as vulcanization accelerator in rubber goods manufacture. Vulcanization transforms the rubber from the thermoplastic into the elastomeric state at temperatures between 150 and 200 °C. CBS is loaded to the rubber in concentrations of 0.5–1% (ww) but it breaks down during the curing process.

Beside CBS, other benzothiazole sulphenamides are used as curing agents. During vulcanization the unstable sulphur-nitrogen link of benzothiazole sulphenamides is split and in a complex reaction sequence the rubber molecules are vulcanized with an intermediate formation of a 2-mercaptobenzothiazole (MBT) radical. Products resulting from the process are basic amines, MBT (partly bound as “pending group”) and secondary reaction products (see section 3.1). The breakdown products are according to experimental data partly included into the rubber matrix and partly released in vulcanization fumes.

The most important products of rubber industry are automobile tires which take about 2/3 of the total rubber production. The remaining rubber is used for various types of “rubber goods”. Of these rubber goods, 65 % of the volume is used in the automotive branch.

3

ENVIRONMENT

3.1

ENVIRONMENTAL EXPOSURE

Environmental releases

The releases of CBS have been estimated for the production sites based on site specific data. The total release of CBS from production to the environment has been estimated at < 1 ton per year. Due to a rapid hydrolysis of CBS, releases of degradation products to water are also expected beside releases of CBS. The generic production site scenario of the TGD does not foresee emissions to air, but the production sites have provided site specific information on their CBS releases to air. Also the provided site specific information on benzothiazole (BT), one of the degradation products, shows that releases to air do occur.

Releases to air from a generic rubber manufacturing site have been estimated according to OECD emission scenario document to be 31 kg/day expressed as unreacted CBS. It is noted, that the major part of this amount is expected to be released in form of breakdown products. In a study investigating losses and analysing substances formed in different type of curing processes, two degradation products of CBS –benzothiazole and 2-methylbenzothiazole- were detected in the process fumes and a weight loss of 0.05 % was observed. At a generic rubber manufacturing site, no releases to waste water are expected.

Based on several studies, the degradation products of CBS can leach or volatilize out of the rubber matrix. Vulcanization products of CBS contained in rubber are released to the environment during their use in tires and rubber goods. The recipient environment for the use in tires is road border soil and surface waters receiving runoff from roads and from road borders. Tire dust entering the European environment contains degradation products of CBS in an amount which corresponds to 1 149 t CBS /a. Households have also been observed to be sources of benzothiazole derivatives. Benzothiazole, 2-benzothiazolone and 2-methylthiobenzothiazole were detected in domestic waste water in Berlin. However, municipal waste water as a collective source of these substances is based on the same study not relevant regarding local risks, although the total release via municipal sewage treatment plants may be relevant for regional exposure.

Releases from processing of used tires (tire shredding) and from uses of recycled rubber occur based on experimental data. BT was found in air in vapour and particulate phase of a tire shredding facility in Taiwan. However, it is not possible to estimate environmental concentrations based on the study. Sites where recycled rubber is used are, e.g., sport halls, asphalt, playgrounds and outdoor sport grounds.

Landfills release CBS degradation products in leachate based on measured data. The source of this release can be assumed to be landfilled tires and rubber goods.

For the degradation products no representative estimate of total or local releases could be calculated so far based on the information on the use volume of CBS, as the formation of each degradation product cannot be quantified.

Environmental fate

The major characteristics of CBS relevant for the exposure assessment are:

- Atmospheric degradation half-life is 0.2 days (estimated)
- Hydrolysis half-life is 12.5 hours (experimental; at pH 7)
- The substance is not readily biodegradable (experimental)
- LogKow is 4.93 (experimental)

The predicted BCF is 3094 and suggests high potential for bioaccumulation, but due to the rapid hydrolysis bioaccumulation in the environment is not likely to occur.

In a standard municipal sewage treatment plant, CBS is expected to be distributed as follows: 33.9 % is directed to water, 54.7 % adsorbed to sludge and 11.4 % are degraded via hydrolysis.

During vulcanization of rubber, several breakdown products are formed from CBS. Partially same substances emerge when CBS degrades in the environment and when the breakdown products in rubber are further degraded in the environment. Table 3.1 presents those degradation products, which are considered most relevant for the environment.

Table 3.1 Relevant degradation products of CBS and their selected environmental properties

	CAS	Molecular weight (g/mol)	Vapour pressure (Pa)	Water solubility (mg/l)	LogKow	BCF	Other
2-Mercaptobenzothiazole (MBT)	149-30-4	167.25	<2.6·10 ⁻⁸ at 25 °C	118 (pH 7; at 25 °C)	ca. 1.4 (around pH 7)	< 8	Weak acid: pKa ≈ 7
<u>2,2'-Dithio-bis-benzothiazole (MBTS)</u>	120-78-5	332.42	5.97·10 ⁻⁸ (at 20 °C)	< 0.2 (at 20 °C)	4.5	≤ 51	
<u>Benzothiazole (BT)</u>	95-16-9	135.19	14	3000 (at 24 °C)	2.0	≤7.5	
<u>2-Benzothiazolone (BTon)</u>	934-34-9	151.19	4.3·10 ⁻⁶	690	1.76	5	
<u>2-Methylthiobenzothiazole (MeSBT)</u>	615-22-5	181.28	0.1024	125 (at 24 °C)	3.1	49	
<u>2-Methylbenzothiazole (MeBT)</u>	120-75-2	149.22	9.47	513	2.47	16	

The same degradation products are released to the environment also from the production and use of other benzothiazole sulphenamides.

MBT is considered not readily biodegradable, although it can be degraded by adapted organisms via methylation to 2-methylthiobenzothiazole (MeSBT) or via oxidation to BTSO₃H and further to 2-benzothiazolone (BTon). MBT is also photodegraded under certain environmental conditions to BT and BTon. MBTS is not readily biodegradable but it is hydrolysed rapidly to MBT. For BT, no definitive conclusion on biodegradation rate can be drawn due to contradictory results. However, the overall rate of degradation is not expected to

be fast as BT is frequently found in the environment. BTon is according to few studies biodegraded when adapted microorganisms are employed. No results from standard biodegradation screening tests are available for the substance. MeSBT has been in few studies observed to resist biodegradation and photolysis. This substance is also found frequently in environmental samples. For 2-methylbenzothiazole (MeBT) no data on degradation are available. The BOWIN v4.02 predicts that the substance is not readily biodegradable.

It is noted, that based on vapour pressure, BT and MeBT are the only substances which can be expected to be emitted in relevant amounts in vapour phase to air.

Environmental concentrations

Due to the fact that the quantities of each degradation product formed from CBS cannot be estimated, the exposure assessment of the degradation products has to rely on measured data.

For the **CBS production sites** aquatic concentrations of CBS and its degradation products were derived based on measured data in the effluents (see Tables 3.4, 3.5). Clocal_{air} of 0.66 µg/m³ for CBS was estimated based on the site specific information provided on the emissions to air. This would correspond to 0.31 µg BT/m³, if it would be assumed, that all CBS degrades in air completely to BT. Regional concentration of CBS in air is negligible (Clocal ≈ PEClocal). The highest measured concentration of BT in air around one production site is 0.03 mg/m³. Clocal_{air} of BT for the other two production sites is ≤ 0.02 µg/m³ based on the information provided on the emissions of BT.

For a generic **rubber manufacturing site**, PEClocal_{air} of 8.62 µg /m³ as CBS -equivalent has been estimated according to the OECD emission scenario document. It is noted, that the majority of this amount is expected to be present as degradation products. Releases to waste water are expected not to occur. A Clocal_{air} of 0.06 µg/m³ has been estimated for BT based on experimental data. No environmental concentration of MeBT has been derived, but it is based on information on MeBT -releases lower than the concentration of BT. The other environmentally relevant breakdown products are due to their low vapour pressure not expected to be relevant for the air compartment.

For water bodies which receive CBS breakdown products from **tire abrasion** from roads and road borders, a tentative PEClocal_{freshwater} has been derived based on measured data for BT (0.6 µg/l), BTon (0.2 µg/l), MeSBT (5.6 µg/l) and MeBT (0.6 µg/l). Accordingly, a tentative PEClocal_{soil} for road borders was derived for BT (336 µg/kg dw), MeSBT (86 µg/kg dw) and MeBT (34 µg/kg dw). It is noted, that the monitoring data are scarce for road borders and further measured data are needed. For road borders, no concentration in air has been derived.

A Clocal_{air} of 0.023 µg BT/m³ has been derived for air around sport halls. The concentration has been derived based on measured data on BT in sport halls in a Norwegian study. This exposure is caused by **recycled tire crumb** in ground material. Other benzothiazole derivatives including CBS were detected in particulate matter from air samples, but the concentrations were so low (< 1 ng/m³), that they are not considered relevant for the risk assessment. Releases from outdoor sport grounds can be expected based on further experimental data from Norway on other substances than benzothiazole derivatives. However, no measured data from surface waters receiving storm runoff from outdoor sport grounds are available for benzothiazoles and therefore no estimate of the local concentration could be derived.

For **landfill** leachate, no local PECs could be derived for the aquatic compartment due to the very few measured data. The available monitoring data, however, indicate, that BT, BTon, MeBT and MeSBT can be present in leachate at levels up to more than hundred µg/l. More measured data are needed to derive a representative PEC. Other compartments than water are not considered as relevant recipients of releases from landfills.

Based on a small set of measured data, regional aquatic PEC has been derived for BT (23 ng/l) and MeSBT (61 ng/l). The corresponding regional PEC_{marine} is for BT 0.82 ng/l and for MeSBT 0.99 ng/l. For other degradation products, no measured data reflecting ambient background concentrations are available.

For the assessment of sediment, see section 3.3.

A PEC_{Coral, fish} of 0.309 mg/kg has been obtained assuming a BCF of 3094 for CBS. Of the degradation products, only MeSBT can be considered relevant regarding the secondary poisoning route. For MeSBT, no appropriate mammalian data are available to derive a PEC_{Coral, fish}. Considering that the estimated BCF of CBS is significantly higher than BCF of MeSBT and that the ecotoxicity of CBS is higher than the ecotoxicity of MeSBT, the assessment of the secondary poisoning route for CBS is assumed to cover also the risks of MeSBT.

3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. sediment)

PNEC –values derived for CBS and its relevant degradation products are presented in Table 3.2.

Table 3.2 Aquatic PNECs of CBS and its degradation products

Substance	PNEC _{water, freshwater} (µg/l)	Available data	PNEC _{water, marine} (µg/l)	PNEC _{microorg} (mg/l)
N-Cyclohexylbenzothiazole-2-sulphenamide (CBS)	0.32	Prolonged test on fish, acute tests on daphnia and algae	0.032	1.9
2-Mercaptobenzothiazole (MBT)	0.82 (e)*	NOECs on long-term toxicity to fish and daphnids	0.082	1.0
2,2'-Dithiobis-benzothiazole (MBTS)	0.6 (n)**	Acute tests on fish, invertebrates and algae.	0.06	1.9
Benzothiazole (BT)	8.1 (e)	Acute tests on fish, invertebrates and algae	0.8	14.8
2- Benzothiazolone (BTon)	16.1 (e)	Acute tests on daphnia and algae	1.6	1.0 ***
2-Methylthiobenzothiazole (MeSBT)	3.4 (e)	Acute tests on daphnia and algae	0.3	1.0 ***
2-Methylbenzothiazole (MeBT)	29.8 (e)	Acute tests on daphnia and algae	3.0	1.0 ***

* (e) indicates that the critical study result refers to effective concentration. ** (n) indicates that the critical study result refers to nominal concentration. *** as a tentative PNEC a read across from PNEC for MBT is used.

For **CBS**, a 14 day LC20 of 0.96 mg/l (measured concentration) is available from a flow-through study with fish *Oncorhynchus mykiss*. For *Daphnia magna*, a 48 hour EC50 of < 18 mg/l (nominal) has been derived. An EC μ 50 < 0.9 mg/l and EC μ 8 < 0.3 mg/l (both nominal concentrations) are available from a 96 hour test with green algae *Selenastrum capricornutum*. The algae test has a good quality regarding the standard requirements, but the result is not reliable because the test is static, the result has been reported as nominal concentration and during the test period a significant hydrolysis is expected to occur. The water solubility limit of 0.32 μ g/l has been chosen to PNEC_{freshwater} as a pragmatic approach and it is flagged as “tentative”. This flag denotes the incompleteness of the data set. However further testing is not required, because due to the fast hydrolysis it is not possible to conduct a reliable algae ecotoxicity test.

For **MBT**, results from long-term tests are available for freshwater species out of 3 trophic levels. An embryo-larval test with *Oncorhynchus mykiss* carried out in a flow-through system resulted in a NOEC of 41 μ g/l. From a flow-through test on *Daphnia magna* a NOEC of 240 μ g/l was obtained, while for algae (*Selenastrum capricornutum*) the NOEC was estimated to < 60 μ g/l (nominal concentration). Because MBT can be expected to be unstable against photolysis in the reported test conditions, the effective concentration may be lower in the algae test. In addition, the acute test results indicate that algae would be the most sensitive group. Due to the considerations above an assessment factor of 50 is applied to the result from the fish test. The PNEC_{freshwater} has been determined to 0.82 μ g/l

For **MBTS**, tests on the acute toxicity to freshwater species out of 3 trophic levels are available from static tests where results have been reported as nominal concentrations. The lowest observed effect value is an EC μ 50 of 0.6 mg/l from a growth inhibition test with the algae *Selenastrum capricornutum*. Using an assessment factor of 1000, the PNEC_{freshwater} is determined to 0.6 μ g/l. It is noted, that due to the instability of MBST, the determined PNEC value probably refers either to suspended MBTS, or its water-soluble impurities, or to MBTS degradation products.

For **BT**, plausible acute tests are available from all three trophic levels. An acute test with lowest result (LC50 = 8.1 mg/l) has been conducted with fish in a flow through test with analytical control. The lowest algae EC50 (50.8 mg/l) has been obtained from a static test with analytical control. The lowest LC50 of two invertebrate tests (20 mg/l) had no analytical control, but due to a short test duration (48 h) and stability of the substance it can be assumed that an appropriate amount of the nominal concentration remained in the solution. The fish study is used for the derivation of PNEC. Assessment factor of 1000 is applied and a PNEC_{freshwater} of 8.1 μ g/l result.

For **BTon**, available test data from a 48 h daphnia immobilisation test (EC50 = 16.1 mg/l) and from a 72 h algal growth inhibition study (E_rC50 = 22.42 mg/l) allow a provisional PNEC derivation. A reservation regards to a lack of any study with fish as a third trophic level and a limited validity of the algae test. However, read-across to other CBS degradation products and CBS provide strong evidence that there is no specific toxicity to any trophic level's standard test species. An assessment factor of 1000 is applied to the daphnia test result. PNEC_{freshwater} = 16.1 μ g/l.

For **MeSBT**, available test data from a 48 h daphnia immobilisation test (EC50 = 8.5 mg/l) and from a 72 h algal growth inhibition study (E_rC50 = 3.43 mg/l) allow a provisional PNEC

derivation. A reservation regards to a lack of any study with fish as a third trophic level and a limited validity of the algae test. However, read-across to other CBS degradation products and CBS provide strong evidence that there is no specific toxicity to any trophic level's standard test species. An assessment factor of 1000 is applied to the algae test result. $PNEC_{\text{freshwater}} = 3.4 \mu\text{g/l}$.

For **MeBT**, available test data from a 48 h daphnia immobilisation test ($EC_{50} = 29.8 \text{ mg/l}$) and from a 72 h algal growth inhibition study ($E_rC_{50} = 32 \text{ mg/l}$) allow a provisional PNEC derivation. A reservation regards to a lack of any study with fish as a third trophic level and a limited validity of the algae test. However, read-across to other CBS degradation products and CBS provide strong evidence that there is no specific toxicity to any trophic level's standard test species. An assessment factor of 1000 is applied to the daphnia test result. $PNEC_{\text{freshwater}} = 29.8 \mu\text{g/l}$.

For the marine PNEC-values an additional assessment factor of 10 has been applied due to the lack of experimental data on marine biota.

For the assessment of sediment, see section 3.3.

An activated sludge respiration inhibition test (OECD 209) has been carried out with a commercial product sample of CBS with an $EC_{50} > 10\,000 \text{ mg/l}$. Reading across from the properties of 2,2'-dithio-bis-benzothiazole (MBTS), inhibition of nitrification in the sewage treatment plant cannot be excluded. There is no study available for this type of effects for CBS. Due to similarities regarding structure and reaction routes, the PNEC for nitrification inhibition from MBTS will be applied for CBS.

Tests on the toxicity to sewage treatment plant micro-organisms are not available for BTon, MeSBT and MeBT. For these substances, the lowest PNEC derived on the basis of test data is applied ($PNEC_{\text{stp,microorg.}}$ for MBT = 1.0 mg/l). For substances, which are most toxic on the basis of ecotoxicity data from aquatic environment and which are expected to show excess toxicity (MBT, MBTS and CBS), $PNEC_{\text{stp,microorg}}$ have been derived from tests. Thus cross-reading to the degradation products BTon, MeSBT and MeBT is considered a rather conservative approach and therefore applied here.

It is noted, that due to the limitations of the aquatic datasets of MBTS, BTon, MeSBT and MeBT, the PNECs derived are a case choice considering the constraints of Regulation 93/793/EEC and applicable for this assessment only.

Terrestrial compartment

There are no test results with CBS available for soil organisms. The $PNEC_{\text{soil}}$ of 70.1 $\mu\text{g/kg}$ wwt was calculated from $PNEC_{\text{water}}$ of 0.32 $\mu\text{g/l}$ according to the equilibrium partitioning method.

Valid tests on soil organisms are not available for the degradation products. $PNEC_{\text{soil}}$ –values derived using the equilibrium partitioning method are presented in Table 3.3.

Table 3.3 $PNEC_{\text{soil}}$ of CBS degradation products

Substance	$PNEC_{\text{soil}}$ (mg/kg wwt)
2-Mercaptobenzothiazole (MBT)	0.0228
2,2'-Dithiobis-benzothiazole	0.059

(MBTS)	
Benzothiazole (BT)	0.0172
2- Benzothiazolone (BTon)	0.0367
2-Methylthiobenzothiazole (MeSBT)	0.0263
2-Methylbenzothiazole (MeBT)	0.109

Atmosphere

CBS is a non-volatile substance and it is released into the atmosphere only in dust form. Tests on plants are not available. Fumigation tests with other benzothiazole derivatives are not available, either.

Secondary poisoning

PNEC_{oral,mammal} = 0.47 mg/kg food has been obtained using the lowest available NOAEL. The NOAEL of 7.1 mg/kg bw/day applied for the PNEC resulted from a developmental repeated dose study with female rats and was based on reductions in body weight gain (maternal endpoint). No ecotoxicity studies on birds are available for CBS.

The stable degradation products of CBS do not show high bioaccumulation potential on the basis of partition coefficients and available studies. Only MeSBT has a logKow above 3, but for this substance, no appropriate dataset on effects from mammals or birds exists. The secondary poisoning assessment of CBS is assumed to represent the worst case for all relevant degradation products.

3.3 RISK CHARACTERISATION

CBS is subject to a rapid hydrolysis and it is emitted to the environment mainly in form of its degradation products from production and from its sole use as vulcanization agent. Therefore in this risk assessment also six environmentally relevant degradation products of CBS have been addressed. Multiple exposure is reflected in a conservative way by applying the additive risk characterisation method proposed in the TGD for petroleum substances. The approach assumes that all substances included in the risk characterisation cause effects with a same mode of action which means that their effects would be additive. CBS, MBT and MBTS are reactive substances, BT, MeSBT and MeBT are neutral organics with baseline (narcotic) toxicity and BTon belongs to the group of thiazolinones with enhanced toxicity. Hence these substances may elicit effects with different mode of actions. Therefore the additive risk characterisation method is assumed to provide conservative estimates of the risks even when considering the limitations of the dataset on aquatic ecotoxicity.

Aquatic compartment (incl. sediment)**Production sites**

Risk ratios and local concentrations of CBS and its environmentally relevant degradation products at the CBS production sites are presented in Tables 3.4 and 3.5. The local concentrations in Table 3.5 are presented as C_{local} , as only for BT and MeSBT (negligible) regional PECs could be derived based on measured data.

Table 3.4 Risk characterisation ratios of CBS for the production sites

Site	Release into	$PEC_{local,water}$ ($\mu\text{g/l}$)	$PEC_{water} / PNEC_{water}$	$C_{effl.}$ ($\mu\text{g/l}$)	$C_{effl.} / PNEC_{microorg.}$
A	river	0.1	0.3	6	0.003
B	river	< 0.13	< 0.4	< 100	0.05
C	river	0.03	0.09	< 10	0.005

Table 3.5 Risk characterisation ratios of degradation products

Substance	Site	$C_{local,water}$ ($\mu\text{g/l}$)	$C_{water} / PNEC_{water}$	$C_{effl.}$ ($\mu\text{g/l}$)	$C_{effl.} / PNEC_{microorg.}$
2-Mercaptobenzothiazole (MBT)	A	< 0.3	<0.37	< 20	< 0.02
	B	0.008	0.009	6.4	0.006
	C	0.478	0.583	183.8	0.18
2,2'-Dithio-bis-benzothiazole (MBTS)	A	< 0.3	<0.5	< 20	<0.01
	B	0.1	0.2	106	0.06
	C	<0.026	<0.04	< 10	<0.005
Benzothiazole (BT)	A	< 0.2	<0.002	< 10	<0.001
	B	0.13	0.02	80	0.005
	C	<0.026	<0.003	< 10	0.001
2-Benzothiazolone (BTon)	A	< 0.2	<0.01	< 10	< 1
	B	0.12	0.007	70	< 1
	C	0.122	0.008	47.0	<1
2-Methylthiobenzothiazole (MeSBT)	A	< 0.2	<0.06	< 10	< 1
	B	0.03	0.009	24	< 1
	C	<0.026	<0.008	< 10	< 1
2-Methylbenzothiazole (MeBT)	A	< 0.2	< 0.007	< 10	<1
	B	0.07	0.002	29	<1
	C	<0.026	<0.001	< 10	<1

The sum of the risk ratios of CBS and the six degradation products (additive risk characterisation method) indicates for **conclusion ii**:

Site A: RCR < 1.25

Site B: RCR < 0.65

Site C: RCR = 0.7

Rubber and tire industry

No releases of CBS or its degradation products are expected occur to the aquatic environment (**conclusion ii**).

Use in tires

Preliminary risk ratios are presented in Table 3.6 for those degradation products, for which measured data were available.

Table 3.6 Risk characterization of CBS breakdown products for use in tires

	Preliminary PEC _{water} (µg/l)	PEC _{water} /PNEC _{water}
Benzothiazole (BT)	0.6	0.07
2-Benzothiazolone (BTon)	0.2	0.01
2-Methylbenzothiazole (MeBT)	0.6	0.02
2-Methylthiobenzothiazole (MeSBT)	5.6	1.65

The provisional PECs have been determined for water bodies receiving runoff from roads and they are based on very scarce data. The additive risk characterisation method results in a **RCR of 1.75**. In addition, methylthiobenzothiazole alone causes risk. More measured data are needed to derive representative PECs (**conclusion i**).

Tire recycling

Results of leaching tests of tires, rubberised asphalt and novel rubber material for sport grounds give reason to expect that runoff discharged to surface waters from sport fields and other outdoor sites using tire crumb in the ground material may cause local risk to aquatic environment. Local assessment could not be conducted for sport fields as direct measured data from runoff or receiving waters are lacking. In addition, information for the estimation of the total release from the use of recycled rubber was not available (**conclusion i**).

Landfills

Based on the available scarce measured data, no conclusions regarding to the exposure level in waters receiving leachate from landfills can be drawn. However, some of the measured concentrations are so high (> hundred micrograms per litre), that risks cannot be excluded. Further measured data are needed (**conclusion i**).

Sediment

Because of the rapid hydrolysis accumulation of CBS in sediments is not expected. Therefore a risk assessment for this sub-compartment is not necessary (**conclusion ii**).

For CBS breakdown products neither representative monitoring data in sediments nor toxicity tests on sediment organisms are available. Both exposure and environmental effects could be estimated using the equilibrium partitioning method. This approach leads to the same PEC/PNEC ratios and conclusions as in the aquatic risk assessment.

Terrestrial compartment

No risks to soil are expected around the production sites and around rubber and tire manufacturing sites due to low emissions and very low concentrations in air (**conclusion ii**).

Risk ratios of substances for which some measured data were available for road border soil (reflecting the risks caused by the use in tires) are presented in Table 3.7.

Table 3.7 Risk characterisation of CBS breakdown products for road border soil based on measured data

Compound	Preliminary PEC _{soil} (µg/kg dw)	PEC/PNEC
Benzothiazole (BT)	336	16.8
2-Methylbenzothiazole (MeBT)	34	0.44
2-Methylthiobenzothiazole (MeSBT)	86	2.9

The additive risk characterization approach gives a **RCR of 20**. BT and MeSBT seem to cause already alone risk at a 5 meter distance of the studied roads. More measured data are needed to refine the PECs and to establish them for the other relevant degradation products (**conclusion i**).

Atmosphere

For the production sites and rubber manufacture the estimated or measured concentrations in air around the sites for CBS, BT and MeBT are so low, that the plant-air route is considered not to be relevant (**conclusion ii**).

Due to a probably high amount of tire recycling activities, regional release of degradation products may be relevant (with regard to deposition). However, due to the lack of information on the total market demand of tire crumb materials, no estimation of total release could be conducted (**conclusion i**).

Secondary poisoning

For water-fish-mammal secondary poisoning route, a RCR of 0.66 has been derived for CBS (**conclusion ii**). The result represents the realistic worst case also for the sum of exposure of the degradation products.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Occupational exposure

In Western Europe N-Cyclohexylbenzothiazol-2-sulfenamide (in the following CBS) is exclusively used as a vulcanisation accelerator in rubber goods manufacture. CBS is produced by four companies in the EU. In 1993 the demand of CBS in Western Europe was estimated to 15,500 t which is about 50 % of the total accelerators demand. The world CBS production is estimated to 44,000 – 45,000 t for 1993. It is expected that the CBS demand will increase in the next years, because CBS in contrast to other vulcanisation accelerators cannot form toxic nitrosamine. There are no additional data available and no consumer products listed in the Swedish product register and in other data bases (e.g. Nordic Product Register SPIN).

Detailed information on the production volumes and the use of CBS is given in chapter 2.

Relevant occupational exposure scenarios are to be expected in the following areas:

- Production of CBS
- Use of CBS as a vulcanisation accelerator in the rubber industry (e.g. rubber goods, tires)

During the vulcanisation (curing) process, CBS like any other vulcanising agent is reacting for at least 95 %. Taking into account that the maximum concentration of CBS in the uncured compounds is 3.5 % (technical rubber), the amount of CBS that can be retained in the finished product is limited to 0.2 %. Due to the resulting low concentration of CBS, a considerable exposure to CBS during the processing of rubber goods is not expected. Therefore, the processing of rubber, e.g. cutting, melting, is not considered in this report.

Occupational exposure limits for CBS have not been established in Western Europe and USA.

The exposure assessment is based on measured data and literature data, expert judgement and estimations according to the EASE model (Estimation and Assessment of Substance Exposure). The exposure levels should be regarded as reasonable worst case estimates representing the highly exposed workers.

CBS is a slight greyish powdery substance (vapour pressure 1.5×10^{-8} hPa at 20°C) which decomposes under the influence of heat. According to information provided by industry CBS is mainly used in dust suppressed forms (granulates or master batches). But the provided information is non-sufficient, so that exposure due to the handling the powdery substance cannot be excluded.

For the large-scale chemical industry, it is assumed that the production and further processing of CBS is mainly performed in closed systems. Storage and conveying CBS is performed in largely automated equipment. Where skin contact can occur, employees are supplied with work dress, safety shoes, gloves and protecting glasses. Exposure occurs if the systems are breached for certain activities, e.g. filling.

As concerning dermal exposure, for the handling of solid substances, as a rule, the suitability of the gloves can be presupposed. This is considered in assessing dermal exposure during production using the EASE model assuming that single dermal contacts can occur although suitable gloves are used.

In the rubber processing industry mainly dust suppressed and to a minor extent powdery CBS are handled. The main source of exposure occurs during emptying scales, weighing and filling. Here it is to be assumed that CBS represents only 10 % of all weighed chemicals and the weighing process is in general an automated process. For this scenario dermal exposure is assessed for the unprotected worker. During the curing process, the majority of the additives are chemically reacting and therefore are no longer present in the finished articles.

Table 4.1.1 Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m ³]	Dermal exposure Shift average [mg/p/day]
1. Production of CBS	shift length, daily	2.0 (workplace measurement, total dust)	42 (EASE, with gloves)
2. Use as a vulcanisation accelerator in the rubber industry	shift length, daily	0.6 ¹⁾ (EASE, low dust material) 1 ²⁾ (analogous data, powdery substance)	200 (analogous data, without gloves)

¹⁾ Use of high amounts of dust suppressed CBS

²⁾ Compared to use of dust suppressed CBS, minor relevant

Consumer exposure

Almost all rubber compounds on the market contain rubber accelerator as CBS in a wide range of products, but it is difficult to know which rubber product contain which rubber accelerants. Therefore the use of CBS in consumer product cannot be ruled out completely. However, based on relevant databases such as SPIN and Nordic database no direct consumer exposure seems to occur. In addition, based on a search in Google, Current Contents and Toxline we found no indication for exposure to CBS through the use of gloves, rubber, toys and household products. Therefore consumer exposure is thought to be minimal and does not need to be further characterized.

Humans exposed via the environment

Total daily intake of CBS via environment is 0.0245 mg/kg bw/day. For benzothiazole, which is one of the environmentally relevant stable degradation products of CBS, a total daily intake of 0.004 mg/kg/day has been calculated.

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

The results after oral administration to rats indicate that CBS is readily absorbed and that intensive metabolism of CBS takes place. As hydrolysis to 2-mercaptobenzothiazol and cyclohexylamine was shown *in vitro* and may occur in the gastrointestinal tract, presystemic metabolism may play a role in the fate of CBS with different kinetic fate of the metabolic breakdown products. Absorption of 100% for the oral route is proposed to be taken for the risk characterisation, whereas dermal and inhalation absorption is assumed to be 100% (defaults).

No data are available for the dermal route. Therefore, a default value for dermal absorption should be applied. Based on the physico-chemical properties of CBS (molecular weight: 264.4 g/mol; log Pow 3.47; water solubility: 0.32 mg/l) a default value of 100% would be derived. However, this default value does not reflect the toxicity data (low toxicity via the dermal route). Therefore, an extent of absorption of 10% will be assumed for dermal risk characterisation purposes.

Acute toxicity

The acute toxicity of CBS in animals is very low after oral and dermal administration; LD50 values of >5000 mg/kg bw were obtained. Data on inhalation toxicity and human data are not available.

Irritation

CBS has demonstrated few cases of skin irritation in human patch tests with the commercial product, when using petrolatum as a vehicle. In animal tests CBS caused slight irritation on the skin and on the conjunctivae of the eye of rabbits. Occasional signs of mild nasal irritation were observed in some Sprague-Dawley CD rats immediately after the 6-hour exposure period with atmospheric concentrations up to 0.048 mg/l CBS 5 days per week in a 28-day inhalation toxicity study. The animals recovered from symptoms within 24 hours and these findings did not correlate to histopathological effects. In light of the fact that CBS has shown slight irritations at the eye of rabbits it seems plausible that CBS leads also to slight irritations at the mucous membranes of the respiratory tract after inhalation. However, these data cannot be used to conclude a potential of CBS to cause acute respiratory irritation relevant for classification and labelling.

Corrosivity

CBS is not a corrosive substance.

Sensitisation

Data on sensitization caused by inhalation are not available. As no cases of respiratory sensitization after occupational exposure have been reported yet, it can be assumed that CBS does not induce sensitization via the inhalation route. CBS did not cause skin sensitization in

guinea pigs. In contrast, there was one well conducted human patch testing study which clearly demonstrated contact sensitization in humans. Data from epidemiological studies are difficult to assess, but also indicate some skin sensitizing potential of CBS. In consequence, existing classification with R 43 is confirmed.

Repeated dose toxicity

Human toxicity data after repeated exposure to CBS is not available.

The data on repeated dose toxicity in experimental animals with CBS included studies with three routes of administration: inhalation, dermal, oral. These studies were accepted for the requirements of the Regulation 793/93/EEC according to the Annex VIIA, 92/32/EEC. So, the available data permit the derivation of a NOAEC for repeated dose toxicity by inhalation, and a NOAEL by dermal exposure and by oral administration.

Repeated exposure by inhalation to 0.048 mg/l CBS for 28 days caused clear increases in hemosiderin deposition in the spleen of female rats, however without any other indications of hemolysis including e.g. changes in hematology or clinical biochemistry parameters. No local effects on the respiratory tract could be observed at this concentration. The aerodynamic diameter (MMAD) of the CBS dust tested was 7.6µm with a GSD of 2.7µm. This distribution of CBS particle sizes was above the recommendations in common inhalation guideline tests. Thus the reliability of the study is limited because inhalation of these CBS particles is reduced compared to particles with a MMAD lower than about 4µm. There is no information available whether a smaller particle size of CBS is known compared to the particle size of CBS in the study of Monsanto (1981a). No systemic or local effects were noted in New Zealand White rabbits after repeated dermal exposure for three weeks with 2000 mg/kg bw/d. The oral administration by gavage of ≥250 mg/kg bw/d CBS for a period of 28 days caused coagulopathy of the blood in male and female Crj:CD (SD) rats and effects in the kidney of males. No relevant systemic toxic effects were observed in male and female rats after oral administration of 80 mg/kg bw/d CBS and no local toxic effects on the digestive tract were determined in animals of both sexes treated with 800 mg/kg bw/d.

No-observed-adverse-effect-level or concentration (NOAEL/NOAEC):

Inhalation

With repeated inhalation exposure to 0.048 mg/l CBS for 28 days clear increases in hemosiderin deposition in the spleen were observed in 5/10 female rats. Such finding was neither observed in the lower test group nor in the internal control group. Therefore, this finding was considered as an exposure-related effect to CBS. Since the observed increase in hemosiderin is determined without any other indications of hemolysis including e.g. changes in hematology or clinical biochemistry parameters, the isolated finding of hemosiderin in the spleen is considered to be of minimal toxicological significance and not indicative of an adverse effect on health. So, the highest tested concentration of 0.048 mg/l is considered as NOAEC for systemic effects. For local effects on the respiratory tract a NOAEC could be derived from the same subacute inhalation toxicity study. No relevant local effects were observed at 0.048 mg/l.

28-day study/ Sprague-Dawley CD rat

NOAEC_{sys, local}: 0.048 mg/l, 6 hours/d, 5 days/week (Monsanto, 1981a)

Dermal

In a subacute dermal toxicity study using doses of 125, 500 and 2000 mg/kg bw/d no systemic or local effects were noted in New Zealand White rabbits after repeated dermal exposure for three weeks with 2000 mg/kg bw/d.

21 day-study/ New Zealand White rabbits

NOAEL_{sys, local}: 2000 mg/kg bw/d (Monsanto, 1981b)

Oral

For the oral route of exposure two subacute oral toxicity studies are available, a feeding study and a gavage study. From the feeding study with Sprague-Dawley CD rats a NOAEL of approximately 250 mg/kg bw/d could be derived based on reduced body weight gain and food consumption. However, no blood biochemistry and hematology parameters were examined, and no histopathology was performed in this feeding study. The gavage study was performed mostly in accordance to the regulation requirements (EEC method B.7) and provided data on hematology, clinical biochemistry, organ weights and incidences of histopathological findings. In a 28-day (gavage) toxicity study signs of coagulopathy of the blood were observed in both male and female Crj:CD (SD) rats. In males shortening of the prothrombine time (statistically significant) was noted after oral administration of ≥ 250 mg/kg bw/d CBS, and in females statistically significant decreased platelet count was noted at 800 mg/kg bw/d. CBS-related effects were present in male and female Crj:CD (SD) rats at ≥ 250 mg/kg bw/d. There were signs of a coagulopathy of the blood in both sexes and effects in the kidney of male rats. No relevant systemic toxic effects were observed in male and female rats after repeated oral administration of 80 mg/kg bw/d CBS. Considering the toxicological relevance of the different NOAELs, the NOAEL_{sys} of 80 mg/kg bw/d seemed to be the most relevant one, because the subacute feeding (28-day) study does not fulfil the EEC Annex V criteria. . In the same study no local toxic effects on the digestive tract were noted in males and females after repeated administration of 800 mg/kg bw/d (NOAEL_{local}).

28-day (gavage) study/ Crj:CD (SD) rat

NOAEL_{sys}: 80 mg/kg bw/d (Chemicals Investigation Promoting Council, 1997c)

NOAEL_{local}: 800 mg/kg bw/d (Chemicals Investigation Promoting Council, 1997c)

A lower NOAEL_{sys} of 7.1 mg/kg bw/d (= 0.01% CBS in the diet) for dams was derived from the results of a developmental study based on reductions in body weight gain (Ema et al., 1989). At present there is no reasonable explanation to the unexpected low LOAEL of 69.6 mg/kg bw/d (= 0.1% CBS in the diet) for weight gain impairment in this dietary study (c.f. 4.1.2.9.2). Two other developmental toxicity studies with gavage administration as well as the above reported guideline according repeated dose toxicity study via gavage (28-day) consistently gave considerable higher LOAEL. Furthermore, weight gain impairment in the study of Ema et al. (1989) did not show a dose response and was not seen at the respective dose level in the two comparable developmental studies as well as in the above reported guideline according repeated dose toxicity study. Thus, the lower maternal NOAEL in the study of Ema et al. (1989) is supposed to be not related to a higher sensitivity of pregnant rats but rather be explained from the administration route or probably the rat strain (Wistar rats (Kar:Wistar, Keri Co., Osaka).

In summary, the NOAEL_{sys} for systemic effects for CBS of 80 mg/kg bw/d was derived from the 28-day (gavage) study in Crj:CD (SD) rats and the most sensitive NOAEL_{sys} of 0.048

mg/l (highest concentration tested; 6h/d, 5 d/wk) from a standard 28-day inhalation study in Sprague-Dawley CD rats, respectively.

On the basis of the data submitted, classification of CBS as “harmful” according to the criteria given in Directive 67/548/EEC is not warranted. Inhalation, dermal and oral route of exposure did not show any local or systemic effect at critical dose levels.

This is supported by repeated dose toxicity data for the hydrolysis products MBT and cyclohexylamine:

In toxicity studies with MBT on different duration of treatment, and in addition in carcinogenicity tests in rats and mice of several strains, body weight reduction and microscopically visible changes in the kidneys were observed. After long-term administration decreased survival was noted in dosed male and female rats given doses up to 375 mg/kg bw/d in female rats and 750 mg/kg bw/d in male rats, and nephropathy in males and ulcers and inflammation in the fore stomach in males and females, respectively. There were no increases of nonneoplastic lesions in mice given up to 375 mg/kg bw/d MBT for a period of two years.

Oral administration of cyclohexylamine (at different doses and exposure levels) in several strains of rats and mice in tests on different duration, revealed that the testes is the most sensitive organ to the toxicological effects of cyclohexylamine. No relevant toxic effects were observed in male and female rats given 600 ppm (approx. 24 mg/kg bw/d in males and 35 mg/kg bw/d in females) in the diet for two years. Cyclohexylamine appeared to be somewhat less toxic in mice. Dietary levels of up to 3000 ppm (approx. 400 mg/kg bw/d) did not influence the mortality, rate of body-weight gain, food and water intake, and hematology parameters in mice treated for 80 weeks. No indications for systemic toxicity were found in Swiss mice after long-term feeding at a dietary concentration of 0.5% cyclohexylamine (approx. 500 mg/kg bw/d).

Mutagenicity

CBS was negative in gene mutation assays employing various tester strains of Salmonella and one of Saccharomyces; also a mouse lymphoma assay was negative. An in vitro chromosomal aberration test gave weak evidence for a clastogenic potential. The only in vivo test (on embryonic mortality) cannot be assessed adequately due to insufficient data reporting. There is no relevant evidence for mutagenicity of CBS. This is supported by genotoxicity data for the hydrolysis products MBT and CHA.

Classification of CBS as a mutagen is not warranted.

Carcinogenicity

The existing two long-term studies on CBS in mice are not in accordance with the current testing procedures as proposed by guidelines on carcinogenicity and/or combined chronic toxicity/carcinogenicity (EEC methods, B.32, 33). However, they are performed in accordance with generally accepted scientific standards. The results have shown that CBS is not carcinogenic in mice at a dose of 95.3 mg/kg bw/d (time-weighted average dose). In addition, the carcinogenicity of the both hydrolysis products, MBT and cyclohexylamine, have been investigated in a number of long-term oral studies, involving a variety of strains of

rats and mice. Results of these animal studies have clearly demonstrated that MBT and cyclohexylamine are not carcinogenic in rats and mice. MBT is not carcinogenic in mice and male rats at a dose of 750 mg/kg bw/d and in female rats at a dose of 350 mg/kg bw/d. Cyclohexylamine is not carcinogenic in rats at doses up to 440 mg/kg bw/d and in mice up to 500 mg/kg bw/d, respectively

Currently, the available data of CBS and its hydrolysis products are insufficient to justify the evaluation as an human carcinogen according to the EEC criteria for classification and labelling requirements for dangerous substances (EEC Directive 2001/59/EEC, Annex VI of the Directive 67/548/EEC). Therefore, there is no need for classification and labelling of CBS as a carcinogen.

Toxicity for reproduction

Fertility

From an oral 28-day repeated dose toxicity test with CBS in rats data on reproductive organ toxicity were available. Atrophy of seminiferous tubuli, hyperplasia of interstitial cells and decrease in epididymal sperm numbers were found at a dose of 800 mg/kg bw/d. No NOAEL could be derived from this study since it was unclear why the histopathological findings only were observed in the recovery group and in one of 12 animals of the highest dose group. Additional data were available from investigations on the products of hydrolysis of CBS. For mercaptobenzothiazole (MBT), there is no indication for reproductive organ toxicity or for functional impairment of reproductive capacity and capability.

From investigations with cyclohexylamine (CHA) with repeated administration over longer periods, testicular effects in terms of weight and morphological changes had been revealed. Tubular atrophy and reductions in spermatogenesis had been demonstrated repeatedly in several independent studies.

A NOAEL/testicular toxicity of 100 mg CHA base/kg bw/day is derived from the 3-months study of Brune et al., 1978, and a NOAEL of 82 mg/kg bw/d from the chronic study of Gaunt et al., 1976. With the assumption of hydrolysis of CBS to equimolar amounts of CHA and MBT and with molecular weights of 99.18 for CHA free base and of 264.5 for CBS these values are converted to a NOAEL/reproductive organ toxicity of 267 mg/kg bw/day (Brune et al., 1978) and 218 mg/kg bw/d (Gaunt et al., 1976) for CBS. The absence of testicular effects at these dose levels is supported by the 28 day study with CBS (Chemicals Investigation Promoting Council, 1997c) showing effects at a dose of 800 mg/kg bw/d, whereas no histopathological effects on testes were found with a dosage of 250 mg/kg bw/d.

Taking into account the available database of both CHA and CBS an overall NOAEL (reproductive organ toxicity) of 218 mg/kg bw/d is recommended for use for quantitative risk assessment of CBS.

Developmental toxicity

The available animal data for the hazard assessment of CBS with respect to developmental toxicity are recruited from experiments with rats with the oral route of exposure. Studies with other routes of administration or with other species were not identified in the available database. Results from the three available oral developmental toxicity studies are summarised in Table 4.6. The studies consistently demonstrated that CBS induces maternal toxicity in

terms of impairment of maternal weight gain during gestation and signs of fetal growth retardation in terms of reduced mean fetal body weight. Fetal body weight impairment, however, was exclusively observed at oral dosages associated with significantly reduced maternal weight gain of 15-30%. A substance-related specific embryotoxic and/or teratogenic potential was not revealed from the available studies. Therefore, there is no need for classification and labelling as a reproductive toxicant with regard to developmental toxicity.

Quantitative risk assessment for CBS with respect to developmental toxicity should be based on the data of the study of Ema et al., 1989, with a NOAEL/developmental toxicity of 70 mg/kg bw/day. However it should be recognised that this recommendation is a rather conservative approach. At present there is no reasonable explanation to the unexpected low LOAEL for weight gain impairment in the dietary study of Ema et al., 1989. Two other developmental toxicity studies with gavage administration and a repeated dose toxicity study via gavage (28 day study) consistently gave considerable higher LOAEL values. The lower maternal NOAEL in the study of Ema et al. (1989) with a 20 day dietary exposure is thus supposed to be not related to a higher sensitivity of pregnant rats but rather be explained from the administration route or probably the rat strain (Wistar rats (Kar:Wistar, Keiri Co., Osaka).

4.1.3 Risk characterisation

Workers

Introduction to occupational risk assessment

There are two relevant exposure scenarios for CBS at the workplace. Exposure routes to be considered are inhalation against CBS dust and skin contact with the powdery substance.

Quantitative human toxicity data are not available, therefore risk considerations and estimations have to be based on animal data which have to be extrapolated accordingly. Default values concerning physiological parameters are taken according the proposal of the TGD. Systemic effects after repeated inhalation exposure and skin sensitisation reflect the most sensitive endpoints.

Based on experimental data, oral absorption is assumed to be 100%. There are no experimental absorption data for dermal and inhalation exposure; for these routes of exposure default values of 100% are proposed.

The comparison of the subacute oral and dermal data indicates that toxic potency of CBS by dermal contact is significantly lower than the corresponding oral toxic potency. By assuming a 100% oral bioavailability this relationship corresponds to a dermal bioavailability of 4% (see data in the CRAR). In order to account for the clear experimental evidence of a lower toxic potency by dermal contact on the one hand and to prevent an underestimation of dermal risk (in case of using the 4% value) on the other hand, a 10% dermal bioavailability percentage might be an adequate assumption for dermal risk assessment.

Table 4.1.3.A Occupational exposure levels and internal body burden (CBS)

Exposure scenario	Inhalation		Dermal contact		Internal body burden		
	mg/m ³	mg/kg/d	mg/p/d	mg/kg/d	Inhalation ⁽¹⁾	Dermal ⁽²⁾	Combined
					mg/kg/d		
1. Production of CBS	2	0.3	42 ⁽³⁾	0.6	0.3	0.06	0.36
2. Use as a vulcanisation accelerator in the rubber industry	1	0.14	200 ⁽⁴⁾	3	0.14	0.3	0.44

⁽¹⁾based on the assumption of 100% bioavailability for inhalation and a breathing volume of 10 m³ per shift

⁽²⁾ based on the assumption of 10% bioavailability following dermal contact

⁽³⁾ EASE (90 % protection by suitable gloves)

⁽⁴⁾ Analogous data (without gloves)

Calculation of MOS values

MOS values are calculated as quotient of experimental NOAEL (or LOAEL) from animal studies and workplace exposure levels. Scientifically based adjustment factors are used for the stepwise extrapolation of animal data to the worker population (e.g. adaptation of scenarios, route-to-route extrapolation, inter- and intraspecies extrapolation, duration adjustment and uncertainty in route-to-route extrapolation and dose-response relationship including severity of effect). The multiplication of these different factors give the reference MOS value as a decision mark for concern. Reference MOS values may be different for each toxicological endpoint.

In a parallel procedure, which gives identical but more direct results, a “critical exposure level” (quotient of experimental NOAEL and the according minimal MOS) is identified for each endpoint, indicating concern if occupational exposure levels exceed this value. In the following risks at the workplace are considered specifically for each toxicological endpoint.

Acute toxicity

Local effects

see irritation, no further information available

systemic effects

conclusion (ii)

There is at present no need for further information and/or testing

Systemic effects (inhalation)

Human or animal data with acute exposure by inhalation are not available. In animals, acute oral toxicity was detected to be very low, with oral LD 50 values reported for rats and mice higher than 5,000 mg/kg.

The result of a 28-day inhalation study is used for the risk assessment of acute toxicity. In this test no adverse systemic effects were reported for the highest dose group of 48 mg/m³. Without any further exposure-related adjustments, this exposure level of 48 mg/m³ is directly used as conservative starting point for acute risk assessment.

Based on an interspecies factor of 2.5 (remaining differences) and an intraspecies factor of 5 a reference MOS of 12.5 is calculated. The corresponding critical inhalation exposure level for acute toxicity in humans calculates to about 4 mg/m³ (48 / 12.5).

The shift average values for inhalation are reported as 1 and 2 mg/m³. The resultant MOS value calculates to 24 resp 48 which are above the reference MOS, thus not leading to concern.

Systemic effects by dermal contact

Acute dermal toxicity is considered to be very low. Also in a 21-day dermal study (see repeated dose toxicity) no signs of systemic toxicity up to a dose of 2,000 mg/kg/day was observed in rabbits. This study is used for acute dermal risk assessment.

Without any further adjustment the NOAEL of 2,000 mg/kg is used as adequate starting point. The default factor for interspecies adjustment for rabbits is 2 • 2.5, possible intraspecies variation is accounted for by a factor of 5. The corresponding reference MOS is 25 (2 • 2.5 • 5). The critical exposure level calculates to 80 mg/kg (2,000/25).

The dermal exposure level for Scenario 1 and 2 are reported to 0.6 resp. 3 mg/kg/day. The corresponding MOS values calculate to 3,333 (2,000 / 0.6) resp. 666 (2,000 / 3) which give no reason for concern

Combined exposure

With reference to the semi-quantitative route-specific risk assessments for acute toxicity (inhalation, dermal) it is considered evident, that combined risk assessment for acute toxicity is mainly triggered by exposure by inhalation and is not significantly influenced by dermal exposure. As for acute inhalation toxicity, no concern is reached for combined exposure.

Irritation and corrosivity

Skin, Eye

conclusion (ii) There is at present no need for further information and/or testing

In human patch tests with the commercial product, CBS has not demonstrated any skin irritation. In animal tests CBS caused slight skin and eye irritation. The observed effects are not considered sufficient for classification. There is no concern for dermal or eye irritation at the workplace.

Respiratory tract

Conclusion (i on hold) There is a need for further information and/or testing.

There is only limited information available about local effects after CBS inhalation. Taking into account the missing irritating potential of CBS in the subacute dermal rabbit study, it is assumed that respiratory tract irritation in the range of airborne CBS concentrations tested is mild. In principle, there is the option that further testing of respiratory tract irritation is necessary. Further testing, however, is not considered of priority, because it is assumed that adherence to the critical CBS exposure level of 2 mg/m³, which is specifically derived for systemic effects, effectively reduces the risk of respiratory tract irritation as well. The highest exposure level to be evaluated is 2 mg/m³ for scenario 1 (production of CBS). This judgement on respiratory tract irritation and the corresponding risk is considered to be adequately expressed as conclusion i (on hold).

Sensitisation

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Skin

In a test with guinea pigs no sensitising properties were detected but a repeated insult human patch test with 51 persons using a 70% preparation of CBS demonstrated contact sensitivity in 5/51 individuals. In addition some of the patients with contact dermatitis did show a positive skin reaction on challenge with CBS in skin tests. Based on these data CBS is classified as a skin sensitizer; an effect threshold cannot be estimated.

Because of relevant personal protection measures, for scenario 1 the risk for skin sensitisation is lower than for scenario 2. However, because the available data do not allow deriving a NOAEL, a general concern is expressed for both scenarios

Respiratory tract

Conclusion (ii) There is at present no need for further information and/or testing.

No information on respiratory sensitisation is available. Some potential of CBS to cause respiratory sensitisation cannot be excluded with certainty since in human skin tests the substance demonstrated allergenic properties. However, because there are no specific case reports on human respiratory sensitisation, concern is not expressed.

Repeated dose toxicity

Local effects by dermal contact

Conclusion (ii) There is at present no need for further information and/or testing.

In a subacute dermal toxicity study using doses of up to 2,000 mg/kg/day no substance-specific systemic or local effects were noted in rabbits. Based on these results conclusion ii is reached.

Local effects by inhalation

Conclusion (i on hold) There is a need for further information and/or testing.

The only information available on local effects by inhalation is already described in the chapter of respiratory irritation. With reference to this chapter, conclusion i (on hold) is drawn for local effects by repeated inhalation as well.

Repeated dose toxicity, systemic effects

Systemic effects by inhalation

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The calculation of the internal starting point is based on an oral rat study, because only testing by the oral route resulted in an experimental effect threshold (oral NOAEL of 80 mg/kg/day, oral LOAEL of 250 mg/kg/day). With the default value of 100% absorption percentage the oral NOAEL of 80 mg/kg/d is transformed to an internal starting point of 80 mg/kg/day.

Assuming a 100% absorption by inhalation, the relevant inhalation dose is identical to the internal starting point of 80 mg/kg/d. The inhalation dose of 80 mg/kg/day is divided by a factor of 0.38 m³/kg (rat breathing volume during 8 hours) and is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. This results in an inhalative starting point of 141 mg/m³ (80 x 1/0.38 x 6.7/10).

The reference MOS consists of the interspecies factor of 2.5 (the factor for allometric scaling is already implicitly applied), the intraspecies factor of 5 and the default factor of 6 for duration adjustment. Thus the reference MOS calculates to 75 (2.5 • 5 • 6). The corresponding critical inhalation level calculates to 2 mg/m³ (141 / 75).

Scenario 1 (production of CBS with an exposure level of 2 mg/m³) is a borderline case. Concern is expressed for this scenario, because uncertainties result from the transformation from oral to inhalation route. For the use of CBS as vulcanisation accelerator (scenario 2) the exposure level of 1 mg/m³ is taken forward to risk characterisation. Conclusion ii for this scenario is considered adequate.

Systemic effects by dermal exposure

Conclusion (ii) There is at present no need for further information and/or testing.

For dermal risk assessment a CBS study with rabbits is available. Experimental animals were exposed daily for 21 days for 6 hours per day to 125, 500 and 2,000 mg/kg/day. No dose-dependent systemic effects were noted. The dermal NOAEL was derived to be 2,000 mg/kg/day, keeping in mind that the “real NOAEL” might be higher than 2,000 mg/kg/day. For MOS calculation, the experimental NOAEL of 2,000 mg/kg/d is directly used as starting point.

The reference MOS consists of the interspecies factor of 5 (a factor of 2 for metabolic rate scaling from rabbit to humans and of 2.5 for remaining interspecies differences), an intraspecies factor of 5 and a factor of 6 for duration adjustment. This gives a reference MOS of 150 ($5 \cdot 5 \cdot 6$).

The corresponding critical dermal exposure level calculates to 13 mg/kg/day ($2,000 / 150$). The highest dermal exposure level at the workplace is 3 mg/kg/day (scenario 2). Based on the considerations outlined above, there is neither concern for scenario 1 (production of CBS) with a dermal value of 0.6 mg/kg/day, nor for scenario 2 (use as a vulcanisation accelerator).

Systemic effects by combined exposure

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

The assessment of systemic effects by combined exposure is based on the subacute oral rat study and on corresponding calculations of internal doses (internal NOAEL and total internal body burden).

The internal starting point (based on the oral data) is 80 mg/kg/day. The reference MOS is calculated to be 300 ($4 \cdot 2.5$ for interspecies differences, 5 for intraspecies differences, and 6 for duration adjustment). The corresponding critical internal exposure level is 0.27 mg/kg/day ($80 / 300$). Total internal body burdens for both scenarios are calculated from external exposure levels and the assumption of 100% systemic availability by inhalation and 10% systemic availability by dermal contact. The comparison of the critical internal exposure level of 0.27 mg/kg/d with the internal body burdens for both occupational scenarios (0.36 and 0.44 mg/kg/d) indicates concern for combined exposure. It is recognized that the concern for both scenarios is borderline.

Mutagenicity

Conclusion (ii) There is at present no need for further information and/or testing.

Based on available data, there is no relevant evidence for mutagenicity of CBS. This is supported by mutagenicity data for the hydrolysis products MBT and CHA.

Carcinogenicity

Conclusion (ii) There is at present no need for further information and/or testing.

Two long-term studies with CBS in mice did not provide evidence for a carcinogenic potential of CBS. Results of experimental studies (mice, rats) with the hydrolysis products of CBS (MBT and CHA) did not result in carcinogenic effects either. Based on these experimental data an occupational risk concerning carcinogenicity is not anticipated.

Toxicity for reproduction

Effects on fertility

Conclusion (ii) There is at present no need for further information and/or testing.

Inhalation

A rat NOAEL of 218 mg/kg/day for testis toxicity is used for risk characterisation, because testis toxicity may lead to impaired fertility in humans. For the oral route a 100% absorption is taken forward to risk characterisation. Thus, the oral NOAEL of 218 mg/kg/day is directly transformed to an internal starting point of 218 mg/kg/day.

The internal NOAEL for testis toxicity is converted into a NOAEC (rat, in mg/m³). Systemic availability by inhalation is assumed to be 100%. The internal NOAEL of 218 mg/kg/day is divided by a factor of 0.38 m³/kg (rat breathing volume during 8 hours) and multiplied by a factor of 6.7/10 (activity-driven differences of respiratory volumes in workers). This results in an adjusted rat NAEC of 384 mg/m³ ($218 \cdot 1/0.38 \cdot 6.7/10$).

The reference MOS consists of an interspecies factor of 2.5 (for remaining differences) and an intraspecies factor of 5. Accordingly the reference MOS results in 12.5 ($5 \cdot 2.5$). The corresponding critical inhalation exposure level calculates to 31 mg/m³ ($384 / 12.5$).

The highest exposure level is 2 mg/m³ for scenario 1. Compared to the critical inhalation exposure level of 31 mg/m³ there is no concern for both scenarios (production of CBS and use as a vulcanisation accelerator).

Dermal contact

For dermal risk characterisation of fertility impairment the internal NOAEL (testis toxicity) of 218 mg/kg/d is transformed to the external dermal starting point. Because of the assumption of a 10% systemic availability by dermal contact, the internal NOAEL (testis toxicity) of 218 mg/kg/d is equivalent to an external dermal starting point of 2,180 mg/kg/day ($218 \cdot 10$).

The reference MOS of 50 consists of the standard interspecies factor of 4 \cdot 2.5 and the intraspecies factor of 5. The corresponding critical dermal exposure level calculates to 44 mg/kg/d ($2,180 / 50$). Since dermal exposure for both exposure scenarios is relatively low, there is no indication of a risk for fertility impairment at the workplace.

Combined exposure

Risk assessment for combined exposure again starts with the internal NAEL of 218 mg/kg/day. The reference MOS of 50 is the same as for dermal risk assessment. The critical internal exposure, which is to be compared to the calculated internal body burden, calculates to 4.4 mg/kg/day ($218 / 50$). There is no additional concern for combined exposure.

Developmental toxicity

Conclusion (ii) There is at present no need for further information and/or testing.

The developmental rat toxicity studies with CBS do not indicate a specific embryotoxic, fetotoxic or teratogenic potential. Because a specific risk of developmental damage is not anticipated, a specific concern for developmental toxicity is not expressed.

Summary of risk characterisation for workers

With respect to systemic effects there is concern for repeated dose toxicity (inhalation) for scenario 1 (production of CBS). The lowest critical endpoint-specific exposure level is 2 mg/m³ which results from systemic effects after repeated inhalation. This level should be used as reference for establishing an occupational exposure limit. It is assumed that adherence to this reference level will effectively minimise the risk for respiratory tract irritation as well.

Based on the marginal information on respiratory tract irritation it is assumed that respiratory tract irritation in the range of CBS concentrations tested is mild. Further testing is not considered of priority, because it is assumed that adherence to the critical CBS exposure level of 2 mg/m³, which is specifically derived for systemic effects, effectively reduces the risk of respiratory tract irritation. Based on these considerations, conclusion i (on hold) was drawn for local effects in the respiratory tract.

Dermal contact is without concern regarding general systemic effects; but may elicit allergic skin reactions due to the skin sensitising potential of CBS. With respect to skin sensitisation, there is a general concern for all dermal exposure scenarios; however, because of routinely implemented control measures, the corresponding concern for scenario 1 (production of CBS) is relatively low.

Table 4.1.3.B summarizes the endpoint-specific and scenario-specific conclusions for CBS.

Table 4.1.3.B Summary on occupational risk assessment

Toxicological endpoints		General conclusion	Exposure Scenarios
Acute toxicity	inhalation	ii	
	dermal	ii	
	combined	ii	
Irritation/ Corrosivity	dermal	ii	
	eye	ii	
	acute respiratory tract	i (on hold)	
Sensitisation	skin	iii	1, 2
	respiratory	ii	
Repeated dose toxicity	inhalation, local	i (on hold)	
	inhalation, systemic	iii	1
	dermal, local	ii	

	dermal, systemic	ii	
	combined, systemic	iii	1 ⁽¹⁾ , 2
Mutagenicity		ii	
Carcinogenicity		ii	
Fertility impairment	inhalation	ii	
	dermal	ii	
	combined	ii	
Developmental toxicity	inhalation	ii	
	dermal	ii	
	combined	ii	

(1) conclusion iii already results from inhalative exposure, therefore no specific concern for the combined exposure scenario is indicated

Consumers

Consumer exposure to this chemical is considered to be negligible.

Therefore human health risk regarding to acute toxicity, irritation, corrosivity, sensitisation, repeated dose toxicity, mutagenicity, carcinogenicity and reproductive toxicity is considered to be negligible.

Humans exposed via the environment

When considering possible risks of CBS to human health arising from indirect exposure via the environment the key areas of concerns may be for repeated dose toxicity, mutagenicity, carcinogenicity, and reproductive toxicity.

Following the exposure estimations for humans via the environment there is no concern for indirect local and regional exposure to CBS.

Combined exposure

[click here to insert text]

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

[click here to insert text]

5 RESULTS

5.1 ENVIRONMENT

Aquatic compartment (incl. sediment)

Conclusion (i) There is a need for further information and/or testing.

Several tire recycling activities have been shown to cause exposure of the environment by benzothiazole derivatives. This exposure could not be quantified on the basis of available information. While tire recycling is increasing, exposure of aquatic and terrestrial environment from these activities should be investigated. These activities are especially tire shredding and uses of tire crumb in ground materials.

A number of benzothiazole derivatives were measured in road runoff, in receiving waters and in road border soil. The substances originate from tire abrasion. The measured data indicate that there may be risk in these receiving environments. The available data are, however, too few and no final conclusions should be based on them. Therefore measured data from water bodies receiving road runoff and soils in the vicinity of roads should be produced.

Landfills are according to the available few studies from leachate a source of benzothiazole derivative releases to aquatic environment. Major sources of these substances are expected to be landfilled general rubber products and already deposited tires. Possible risks cannot be excluded due to the scarce and variable data. Measured data are needed to draw conclusions for landfills in general.

In most of the scenarios chronic ecotoxicity data on MeSBT, MeBT, BT and BTon might be able to refine the risk ratios. However, such tests should be considered only after the above required information is made available.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion concerns CBS emissions from the three CBS production sites to the aquatic environment as a source of CBS and waste water treatment plants of the sites. The conclusion also covers the secondary poisoning route of CBS with present exposure levels.

In addition, the combined exposure of CBS and its breakdown products in the aquatic environment and waste water treatment plants does not cause risks at any producer site. In rubber industry, no releases of vulcanisation agents to the surface waters occur. Consequently, no risks for aquatic environment are expected.

This conclusion covers also the exposure of soil for the CBS production and rubber industry (emissions to air).

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Conclusion (i on hold) There is a need for further information and/or testing.

For respiratory tract irritation a conclusion i (on hold) was drawn.

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Two occupational exposure scenarios have been identified: (1) production of CBS in the large-scale chemical industry and (2) the use of CBS as vulcanisation accelerator in the rubber industry.

For CBS, systemic toxicity by repeated inhalation and skin sensitisation are the most relevant toxicological endpoints. With respect to systemic effects there is concern for repeated dose toxicity by inhalation for scenario 1 (production of CBS). The critical exposure level of 2 mg/m³, which is derived for systemic effects by repeated inhalation, is proposed as reference for establishing an occupational exposure limit. It is assumed that adherence to this reference level will effectively minimise the risk for respiratory tract irritation as well.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.