Benzothiazole-based Thiazoles
Category Justification and Testing Rationale

CAS Nos.: **95-32-9; 149-30-4; 155-04-4; 2492-26-4**
(+ SIDS Chemicals 95-16-9 and 120-78-5 for data purposes)

Rubber and Plastic Additives Panel
American Chemistry Council
November, 2001

List of Member Companies in the Rubber and Plastic Additives Panel

The Rubber and Plastic Additives Panel of the American Chemistry Council include the following member companies: Bayer Corporation, Ciba Specialty Chemicals Corporation, Crompton Corporation, Flexsys America L.P., The Goodyear Tire & Rubber Company, The Lubrizol Corporation, Noveon, Inc., R.T. Vanderbilt Company, Inc., and UOP, LLC.

Executive Summary

The American Chemistry Council's Rubber and Plastic Additives Panel (RAPA), and its member companies, hereby submit for review and public comment their test plan for the Benzothiazole-based Thiazoles category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program.

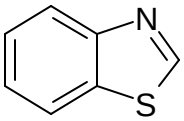
As discussed in the report that follows, Benzothiazole-based thiazoles , which are used primarily as cure- rate accelerators in natural and synthetic rubbers or as chemical intermediates in the manufacture of rubber accelerators, are defined as possessing a benzothiazole backbone [benzene ring + thiazole ring] with various substitutions at the #2 position on the thiazole ring. Their use in the rubber vulcanization process requires stability at high temperatures, low biodegradation, negligible water solubility and low vapor pressure. Non-rubber applications for this category include metal chelation, ore flotation, corrosion inhibition, veterinary drugs and industrial biocide/water treatment for 2-mercapto-benzothiazole and sodium 2-mercaptobenzothiazole.

In consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals, the Panel has conducted a thorough literature search for all available data, published and unpublished. It has also performed an analysis of the adequacy of the existing data. Further, it developed a scientifically supportable category of related chemicals and used structure-activity relationship information to fill certain data gaps. Existing data for members of this category indicate that they are of moderate concern for aquatic toxicity, low concern as Persistent Organic Pollutants (POP), moderate concern for skin irritation/allergic skin reaction, and low concern for mammalian toxicity and carcinogenicity. In addition, the Food and Drug Administration has approved several food-contact uses for this category of chemicals. We conclude that there is sufficient data on the members of this category for purposes of the HPV Program and no additional testing is recommended.

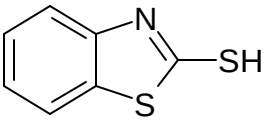
Benzothiazole-based Thiazoles category

As defined by EPA under the HPV Chemical Program, a chemical category is "a group of chemicals whose physico-chemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." The similarities should be based on a common functional group, common precursors or breakdown products (resulting in structurally similar chemicals) and an incremental and constant change across the category. The goal of developing a chemical category is to use interpolation and/or extrapolation to assess chemicals rather than conducting additional testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

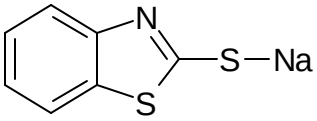
Relying on several factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program,"[1] in which use of chemical categories is encouraged, the following closely related chemicals constitute a chemical category:



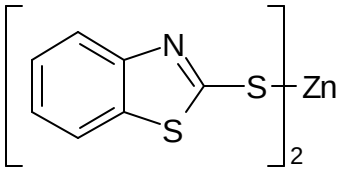
95-16-9
Benzothiazole (BTH)



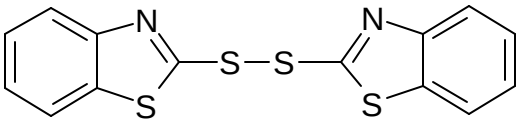
149-30-4
2-Mercaptobenzothiazole (MBT)



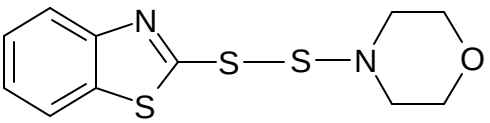
2492-26-4
Sodium 2-mercaptobenzothiazole (NaMBT)



155-04-4
Zinc 2-mercaptobenzothiazole (ZMBT)



120-78-5
Benzothiazole disulfide (MBTS)



95-32-9
Benzothiazole, 2-(4-morpholinyldithio)- (MORFAX)

Figure 1. Chemical structures

[1] US EPA, Office of Pollution Prevention and Toxics. Development of Chemical Categories, Chemical Right-to-Know Initiative. http://www.epa.gov/opptintr/chemrtk/categuid.htm

Structural Similarity

A key factor supporting the classification of these chemicals as a category is their structural similarity. All materials in this category contain the benzothiazole backbone [benzene ring + thiazole ring] with various substitutions on the #2 carbon of the thiazole ring.

Common Precursors

Starting materials and the reaction process are identical for all category members. Aniline, carbon disulfide and sulfur are reacted to form crude 2-mercaptobenzothiazole and benzothiazole. All remaining category members are produced in step-wise batch reactions from this crude 2-Mercaptobenzothiazole.

Common Breakdown Products

2-mercaptobenzothiazole is formed when these compounds undergo hydrolysis and/or dissociation.

Similarity of Physicochemical Properties

The similarity of the physicochemical properties of these materials parallels their structural similarity. All exhibit limited water solubilities, low vapor pressures, high flash points, high boiling points, excellent thermal stability, lack of reactivity, and Log P values at or below 5.

Table 1. Physico-chemical Properties

Chemical **CAS#**	Benzothiazole **95-16-9**	2-Mercapto benzothiazole **149-30-4**	Sodium 2-mercapto benzothiazole **2492-26-4**	Zinc mercapto Benzothiazole **155-04-4**	Benzothiazole 2-(4-morpho linyldithio)- **95-32-9**	Benzothiazole Disulfide **120-78-5**
Molecular Weight:	135.18	167.24	167.24	397.7	284.42	332.38
Melting Point	2°C	181°C	85.8°C (EPI)	233° C (EPI)	173°C (EPI)	180°C
Boiling Point	230°C	decomp above 260°C	301°C (EPI)	544.40°C (EPI)	418.3°C (EPI)	decomp
Relative Density	1.246g/cm3 @20°C	1.42g/cm3 @20°C	1.25g/cm3 @25°C	1.7g/cm3	1.51g/cm3	1.54g/cm3 @25°C
Vapour Pressure	0.13 hPa @20°C	3.0 x10(-6) hPa @25°C	6.0 x10(-4) hPa @25C (EPI)	1.546 x10(-11) hPa @25°C (EPI)	1.16 x10(-7) hPa @25°C (EPI)	5.97 x10(-10) hPa @20°C
Partition Coefficient	2	2.4 (2.86 EPI)	2.4	5.0 (EPI)	1.59 (EPI)	4.5 (4.66 EPI)
Water Solubility	3g/l @20°C	118mg/l @25°C pH 7.0	>500 mg/l @25°C pH12.5	90.9 mg/l @20°C	657.6 mg/l @25°C (EPI)	80 – 96 mg/l @22°C pH 5.0

= Non-sponsored chemicals used for data purposes only

EPI = EPIWin Modeling Program. Meylan W. and Howard P. (1999) Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

Fate and Transport Characteristics

Test data indicate that members of this category are not readily biodegradable when measured by CO_2 evolution, mineralization or hydrolysis, and marginal by indirect photolysis. For purposes of the HPV Program, additional testing is not needed. Testing has shown that, if hydrolysis occurs, the primary hydrolysis product is 2-MBT. Adequate information regarding photodegradation is available, so additional data collection efforts are not necessary. Fugacity modeling has been done for all members of the category and in practice have been shown not to partition to water or air if released into the environment due to their low water solubility and low vapor pressure. (See Table 2)

Toxicological Similarity

Review of existing published and unpublished test data for Benzothiazole-based Thiazoles shows the *aquatic and mammalian toxicity* among the materials within this category are similar. The sodium and zinc salts are expected to immediately dissociate and form mercaptobenzothiazole in an aqueous environment. Studies demonstrate that the salts are less toxic than mercaptobenzothiazole (acute fish toxicity, Daphnia EC50, and acute oral toxicity in rats).

Aquatic Toxicology - Acute

Data on acute fish toxicity, acute invertebrate toxicity, and algal toxicity were reviewed. The Benzothiazole-based Thiazoles range from highly toxic to practically non-toxic. Acute studies on *Pimephales* promelas demonstrate a 96-hour LC_{50} ranging from 11 mg/l (#149-30-4) to greater than 1000 mg/l (#120-78-5). Acute studies on *Daphnia magna* demonstrate a 48-hour EC_{50} ranging from 4.1mg/l (#149-30-4) to greater than solubility range (#120-78-5). Acute studies on Algae demonstrate a 96-hour EC_{50} ranging from 0.25 mg/l (#149-30-4) to greater than solubility range (#120-78-5). Data are available for most chemicals in this category and ECOSAR modeling data is available for the others; therefore sufficient data is available to adequately evaluate the toxicity to aquatic organisms. For purposes of the HPV Program, no additional ecotoxicity toxicity testing is necessary. (See Table 3)

Mammalian Toxicology - Acute

Data on acute mammalian toxicity were reviewed, and the findings indicate a low concern for acute toxicity for all materials. Data are available for most members of the category by the oral and dermal routes of exposure, and inhalation exposure testing has been done on three members of the category, indicating that the category has been well tested for acute mammalian effects. Therefore, for purposes of the HPV Program, no additional acute mammalian toxicity testing is necessary. (See Table 4)

Mammalian Toxicology - Mutagenicity

Data from bacterial reverse mutation assays, *in vitro* and *in vivo* chromosome aberration studies, as well as additional supporting *in vitro* and *in vivo* genetic toxicity studies were reviewed, and the findings indicate a low

concern for mutagenicity. Data are available for all members of the category in the Ames assay. Data are available for all but one chemical for chromosome aberration studies, and these data can be bridged to the other member of the category. There are also carcinogenicity studies available and summarized in the IUCLID documents. Therefore, the category has been adequately tested for mutagenicity for the purposes of the HPV Program, and no additional mutagenicity testing is necessary. (See Table 4)

Mammalian Toxicology – Repeated Dose Toxicity

Data from repeated-dose toxicity studies were reviewed. CAS# 149-30-4 has 28 day, 90 day and chronic studies, which can be bridged to the salts (#155-04-4 and #2492-26-4). There is also a 90 day and chronic study on CAS# 120-78-5. Sufficient data are available to adequately characterize the repeated dose toxicity of this category through bridging to members without test data, such that for purposes of the HPV Program, additional testing is not necessary for these materials. (See Table 4)

Mammalian Toxicology - Reproductive and Developmental Toxicity

There are several adequate reproductive/developmental studies for members of this category. A 2-generation study on CAS# 149-30-4 can be bridged to the salts (#155-04-4 and #2492-26-4). There is also a study on CAS# 120-78-5. Sufficient data are available to adequately characterize the Reproductive and Developmental toxicity of this category through bridging to members without test data. Additional testing will not provide useful and relevant information for this category, therefore for purposes of the HPV Program, testing is not necessary. (See Table 4)

Epidemiology

Two long-term mortality studies have been published on men employed in the production of MBT, MBTS, NaMBT and ZMBT at manufacturing sites in the USA and Europe.
The European study followed 2160 men employed since 1955 and with at least six months exposure to this category of chemicals. The American study followed 1059 employees with a similar work history. There were no statistically significant increases in types of cancer, cancer rates or cancer deaths that could be attributed to chemicals from this category.

Conclusion

Based upon the data reviewed in the report, the reaction routes, the precursors, the physicochemical and toxicological properties of the proposed Benzothiazole-based Thiazoles category members are similar and follow a regular pattern as a result of that structural similarity. Therefore, the EPA's definition of a chemical category has been met.

Test Plan

The test plan for the Benzothiazole-based Thiazoles category was developed giving careful consideration to the number of animals that would be required for any tests that are not available for certain members of the category and whether these additional tests would provide useful and relevant information. We conclude that there is sufficient data on the members of this category for the purposes of the HPV Program, and no additional testing is recommended. (See Table 5)

Table 2. Matrix of Available and Adequate Data on Benzothiazole-based Thiazoles Category
Environmental Fate

Endpoint	Benzothiazole 95-16-9 (SIDS)	2-Mercapto benzothiazole 149-30-4	Sodium 2-mercapto benzothiazole 2492-26-4	Zinc mercapto Benzothiazole 155-04-4	Benzothiazole 2-(4-morpho linyldithio)- 95-32-9	Benzothiazole Disulfide 120-78-5 (SIDS)
Hydrolysis	No data	0-15 % after 7D	No data	No data	No data	37% after 7 D
Biodegradation	0% after 28 D (100 mg/l) >65% after 21 D (0.8mg/l)	< 1 % after 28 D	No data	No data	No data	0.2 % after 28 D
Photodegradation	T ½ = 4.5D	T ½ = 3.2 hr (indirect) T ½ = 0.5 hr (direct)	T ½ = 3.2 hr	T ½ = 1.4 hr	T ½ = 0.37 hr (indirect)	T ½ = 0.4 hr
Fugacity Level III (distribution)						
Air	2.9 %	0.507 %	0.507 %	0.132 %	< 0.1 %	< 0.1 %
Water	40.2 %	35.9 %	35.9 %	19.1 %	36.6 %	17.2 %
Soil	56.8 %	63.4 %	63.4 %	55.9 %	63.3 %	72.7 %
Sediment	0.122 %	0.172 %	0.172 %	24.9 %	0.09 %	10.2%

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Table 3. Matrix of Available and Adequate Data on Benzothiazole-based Thiazoles Category
Ecotoxicity

Endpoint	Benzothiazole **95-16-9**	2-Mercapto benzothiazole **149-30-4**	Sodium 2-mercapto Benzothiazole **2492-26-4**	Zinc mercapto Benzothiazole **155-04-4**	Benzothiazole 2-(4-morpho linyldithio)- **95-32-9**	Benzothiazole Disulfide **120-78-5**
Acute Fish Toxicity (96 hr LC50)	*P. promelas* 64 mg/l *B. rerio* 65.5-66 mg/l	*P. promelas* 11 mg/l *B. rerio* 0.8 – 3.2 mg/l	*L. macrochirus* 12-15 mg/l *O. mykiss* 2.58-3.16 mg/l	*L. idus* 10-50 mg/l (48 hr)	Fish 512 mg/l (ECOSAR)	*P. promelas* > 1000 mg/l *O. mykiss* 66 mg/l
Acute Invertebrate Toxicity (48 hr LC50)	No data	*Daphnia* 2.9 - 4.1 mg/l	*Daphnia* 19 mg/l	*Daphnia* 0.54 mg/l (ECOSAR)	*Daphnia* 533 mg/l (ECOSAR)	*Daphnia* > solubility
Algal Toxicity (96 hr EC50)	No data	*S. capricornutum.* 0.25 mg/l	*S. capricornutum.* 0.3 mg/l	Green Algae 0.420 mg/l (ECOSAR)	Green Algae 325.5 mg/l (ECOSAR)	*S. subspicatus* > solubility

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ECOSAR = Modeling Program - version 0.99e. Meylan W. and Howard P. (1999) Syracuse Research Corporation. Environmental Science Center, 6225 Running Ridge Road, North Syracuse, NY 13212-2510.

Table 4. Matrix of Available and Adequate Data on Benzothiazole-based Thiazoles Category
Mammalian Toxicity

Endpoint	Benzothiazole **95-16-9**	2-Mercapto benzothiazole **149-30-4**	Sodium 2-mercapto benzothiazole **2492-26-4**	Zinc mercapto Benzothiazole **155-04-4**	Benzothiazole 2-(4-morpho linyldithio)- **95-32-9**	Benzothiazole Disulfide **120-78-5**
Acute Toxicity						
Oral LD50	177-479 mg/kg bw (rat)	2830 – 3800 mg/kg bw (rat)	5200 mg/kg (rat) (45-50% substance content)	> 10000 mg/kg bw (rat)	No data	> 7940 mg/kg bw (rat)
Dermal LD50	933– 1233 mg/kg bw (rat)	> 7940 mg/kg bw (rabbit)	> 5010 mg/kg bw (rabbit) (45-50% substance content)	> 7940 mg/kg bw (rabbit)	No data	> 7940 mg/kg bw (rabbit)
Inhalation LC50	ca. 5 mg/l (4 hrs) (rat)	> 1.27 mg/l (4 hrs) (rat)	> 8.2 mg/l (6 hrs) (rat) (22% substance content)	No data	No data	No data
Mutagenicity – gene mutation	Ames = negative	Ames = negative Yeast = negative *E. coli* = negative	Ames = negative Balb3T3 = negative Yeast = negative	Ames = negative Yeast = negative	Ames = negative Balb3T3 = negative	Ames = negative *E. coli* = negative
Mutagenicity – chromosome aberration	No data	MLA = negative Dominant Lethal = negative MNT = negative	No data	No data	No data	MLA = negative
Repeated Dose	No data	90 D NOAEL = 375 mg/kg bw (rat) 28 D NOAEL = 714 mg/kg (rat)	No data	No data	No data	17 month NOAEL = 237 – 464 mg/kg bw (mouse) 90 D NOAEL – 100 mg/kg bw (rat)
Reproductive Toxicity	No data	NOAEL P, F1,F2= < 179 mg/kg bw Repro NOEC = 1071 mg/kg bw (rat)	No data	No data	No data	LOAEL = 200 mg/kg bw (rat)
Developmental Toxicity	No data	NOAEL = 1800 – 2200 mg/kg bw (rat)	No data	No data	No data	NOEL = 596 mg/kg bw (rat)

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Table 5. Test Plan for the Benzothiazole-based Thiazoles Category

Endpoint	Benzothiazole 95-16-9	2-Mercapto benzothiazole 149-30-4	Sodium 2-mercapto Benzothiazole 2492-26-4	Zinc mercapto Benzothiazole 155-04-4	Benzothiazole 2-(4-morpholinyldithio)- 95-32-9	Benzothiazole Disulfide 120-78-5
Environmental Fate						
Hydrolysis	N	A	C	C	C	A
Bio-degradation	A	A	C	C	C	A
Photo-degradation	A	A	A	A	A	A
Fugacity	A	A	A	A	A	A
Ecotoxicology						
Acute Fish Toxicity	A	A	A	A	S	A
Acute Invertebrate	N	A	A	S	S	A
Alga Toxicity	N	A	A	S	S	A
Mammalian Toxicology						
Acute Toxicity	A	A	A	A	C	A
Mutagenicity : gene mutation	A	A	A	A	A	A
Mutagenicity: chromosome	N	A	C	C	C	A
Repeated Dose	N	A	C	C	C	A
Reproductive Toxicity	N	A	C	C	C	A
Developmental Toxicity	N	A	C	C	C	A

= Non-sponsored chemicals used for data purposes only

Key for symbols in table:
A = Adequate data available
C = Use of Category Approach
T = Testing to be done
S = Structure activity relationship
N = No testing; SIDS chemical

Background Information: Manufacturing and Commercial Applications

Manufacturing

The Benzothiazole-based Thiazoles are all made in batch processes using Carbon Disulfide, Aniline and Sulfur as starting materials. That reaction produces Crude MBT (90%) and BTH (5%). Crude MBT is treated with aqueous Sodium Hydroxide to produce NaMBT. The NaMBT solution is reacted with Zinc Sulfate to produce ZMBT, Sulfuric Acid to produce purified MBT, and Chlorine to produce MBTS. MBTS is reacted with Morpholine and additional Sulfur to produce MORFAX.

Commercial Applications

Benzothiazole-based Thiazole rubber chemicals have been manufactured in the United States since the late 1920s, and are widely used throughout the industry due to their excellent stability, functionality and low cost. Over 90% of all usage is as cure-rate accelerators in the manufacture of tires (sidewall, tread and retread, carcass, belt skim, liner, bead filler/chafer, and base tread) and industrial rubber products (automotive extruded sponge, latex and foam, insulated wire, insulation jackets, molded and mechanical goods). Latex applications include shoe soles, elastic, carpet backing, gloves and tubing. The typical usage for a cure-rate accelerator application ranges from 0.5 to 5 parts accelerator per 100 parts of rubber (phr). The Specialty Chemical (non-rubber) applications include chemical intermediates for rubber additives, herbicides and pharmaceuticals, as industrial water treatment additives, for ore chelation/flotation/separation, lubrication additives, as a corrosion inhibitor in ethylene glycol-based automotive antifreeze and as topical veterinary drugs.

Compounds in this category are sold only to large industrial users as ingredients or reagents for their products or processes. There are no direct consumer applications for this class of compounds, and therefore no direct sales to the general public.

The following chemicals have been “Regulated for Use” by the Food and Drug Administration in various food-contact applications:

175.105	Components of Adhesives	MBT, ZMBT, MBTS, NaMBT
176.200	Defoaming Agents, Coatings	NaMBT
176.210	Defoaming Agents, Paper	NaMBT
176.300	Slimicides	MBT
177.2600	Rubber Articles	MBT, ZMBT, MBTS
178.3120	Animal Glue	ZMBT, NaMBT

Shipping/Distribution

Benzothiazole-based thiazole compounds are shipped extensively throughout the world from manufacturing plants located in the United States, South America, Eastern and Western Europe, Japan and China.

Worker/Consumer Exposure

The rubber and plastics additives industry has a long safety record and only sophisticated industrial users handle these materials. Exposure of workers handling Benzothiazole-based thiazole materials is likely to be the highest in the area of material packaging rather than from chemical manufacturing. These materials are made as pastilles (pellets), powders, flakes, solids and liquids. Product forms that minimize dust generation, coupled with the mechanized materials handling systems of the large industrial users, combine to keep exposures to minimum levels. However, during material packout at the manufacturing site and, to a somewhat lesser degree during weigh-up activities at the customer site, there is a potential for skin and inhalation exposure (nuisance dust is the primary route of worker exposure) and also dermal contact with liquid forms.

Consumer exposure is minimal. Only very small amounts are used in rubber processing, and the materials themselves become bound in the rubber matrix during the vulcanization process. The most likely route of consumer exposure is skin contact from rubber or latex articles. Skin irritation, or possibly an allergic skin reaction may occur, but only in sensitive individuals subjected to prolonged and repeated exposure, especially under moist conditions. In the specialty application of ethylene glycol-based automotive antifreeze, the amount used is less than 3%.