Revised Benzothiazole-based Thiazoles Category Justification and Testing Rationale

CAS Nos.: 149-30-4; 155-04-4; 2492-26-4

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Rubber and Plastic Additives Panel of the
American Chemistry Council
Revised July 2003

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: Alco Chemicals; Bayer Polymers LLC.; Ciba Specialty Chemicals Corporation; Crompton Corporation; Eliokem, Inc.; Flexsys America L.P.; The Goodyear Tire & Rubber Company; The Lubrizol Corporation; Noveon, Inc.; and, R.T. Vanderbilt Company, Inc.

Executive Summary

The American Chemistry Council's Rubber and Plastic Additives Panel (RAPA), and its member companies, hereby submit the test plan for the revised Benzothiazole-based Thiazoles category of chemicals under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program. The documents submitted in support of the category (dated November 30, 2001), as originally conceived, included data for 2-(4-morpholinyldithio)-benzothiazole (CAS number 95-32-9). Comments received from EPA dated September 6, 2002 questioned whether the data supported extrapolation across the category. Accordingly, revised test plans and robust summaries for the four chemicals that were formerly included in the *Benzothiazole-based Thiazoles* category are being resubmitted to include the three chemicals in the revised *Benzothiazole-based Thiazoles* category that are the subjects of this document and the fourth chemical in separate documents describing the *Benzothiazole and Morpholine-based Thiazole* category.

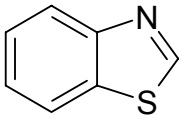
As discussed in the report that follows, Benzothiazole-based Thiazoles , which are used primarily as cure-rate accelerators in natural and synthetic rubbers or as chemical intermediates in the manufacture of rubber accelerators, are defined as possessing a benzothiazole backbone [benzene ring + thiazole 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 an extensive 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 address certain data requirements. 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 U.S. 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.

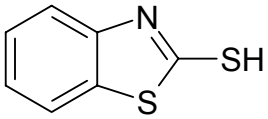
Benzothiazole-based Thiazoles Category

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 unnecessary testing with specific consideration of animal welfare concerns to minimize the use of animals in the testing of chemicals.

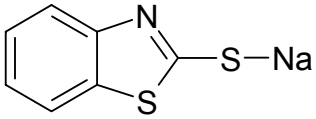
Relying on several factors specified in EPA's guidance document on "Development of Chemical Categories in the HPV Challenge Program,"[1] in which use of chemical categories is encouraged, the following closely related chemicals constitute a chemical category:



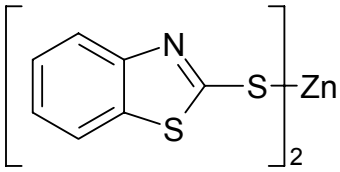
95-16-9
Benzothiazole (BTH)



149-30-4
2-Mercaptobenzothiazole (MBT)



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



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

Figure 1. Chemical structures

Structural Similarity

[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.

A key factor supporting the classification of these chemicals as a category is their structural similarity. The materials in this category contain the benzothiazole backbone [benzene ring + thiazole ring] with various substitutions on the #2 carbon of the thiazole ring. In addition, the chemicals are similar in that they are 2- mercaptobenzothiazole and the sodium and zinc salts. The EPA, Office of Prevention, Pesticides and Toxic Substances, has grouped MBT and its salts in the Reregistration Eligibility Decision (RED) document, EPA 738-F-94-024, and uses the toxicity studies of MBT to cover the endpoints of the salts.

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

Mercaptobenzothiazole is formed when the sodium and zinc salts undergo hydrolysis and/or dissociation.

Physicochemical Properties

The sodium salt (NaMBT) is water soluble and it is commercially supplied as an aqueous solution; the vapor pressure listed is due to the water present in the aqueous solution. 2-mercaptobenzothiazole (MBT) and the zinc salt (ZMBT) 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. No additional testing is necessary, for purposes of the HPV Program (See Table 1).

Table 1. Physico-chemical Properties

Chemical **CAS#**	**2-Mercaptobenzothiazole (MBT)** **149-30-4**	**Zinc mercapto Benzothiazole (ZMBT)** **155-04-4**	**Sodium 2-mercapto Benzothiazole (NaMBT)** **2492-26-4**
Molecular Weight	167.24	397.7	189.23
Physical state	Solid	Solid	Liquid
Melting Point	181˚C	337˚ C	- 6 ˚C
Boiling Point	decomp above 260˚C	361.8˚C @38.66 hPa	103˚C @1013 hPa
Relative Density	1.42g/cm3 @20˚C	1.7g/cm3	1.25g/cm3 @25˚C
Vapour Pressure	3.0 x10(-6) hPa @25˚C	1.546 x10(-11) hPa @25˚C (EPI)	**34.26 hPa @30˚C**
Partition Coefficient	2.4 (2.86 EPI)	5.0 (EPI)	**- 0.46**
Water Solubility	118mg/l @25˚C pH 7.0	90.9 mg/l @20˚C	>500 mg/l @25˚C pH12.5

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 MBT. Adequate information regarding photodegradation is available, so additional data collection efforts are not proposed. Fugacity modeling has been done for all members of the category and in practice, MBT and ZMBT 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. NaMBT is expected to partition to water and discharge of effluent into surface waters is monitored and limited (See Table 2).

Aquatic Toxicology - Acute

Data on acute fish toxicity, acute invertebrate toxicity, and algal toxicity were reviewed. NaMBT has adequate acute aquatic studies. Acute studies on *Pimephales promelas* demonstrate a 96-hour LC_{50} of 11 mg/l (MBT) and 10-50 mg/l (ZMBT). Acute studies on *Daphnia magna* demonstrate a 48-hour EC_{50} of 2.9 mg/l (MBT) and on Algae a 96-hour EC_{50} of 0.25 mg/l (MBT). By comparing the similarity of fish toxicity results, the invertebrate and algae toxicity of ZMBT is expected to be at least as toxic as MBT. 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 all members of the category by the oral and dermal routes of exposure, and inhalation exposure testing has been done on two 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 MBT and ZMBT for chromosome aberration studies, and these data can be bridged to NaMBT. There are also carcinogenicity studies available and summarized in the IUCLID documents. Therefore, the category has been adequately tested for mutagenicity, for purposes of the HPV Program, and no additional mutagenicity testing is proposed (See Table 4).

Mammalian Toxicology – Repeated Dose Toxicity

Data from repeated-dose toxicity studies were reviewed. There are subchronic and chronic studies on all members of the group, therefore, for purposes of the HPV Program, additional testing on this endpoint is not necessary for these chemicals (See Table 4).

Mammalian Toxicology - Reproductive and Developmental Toxicity

There is an adequate 2-generation, reproductive/developmental study for MBT which can be bridged to the salts (NaMBT and ZMBT). Additional testing is not expected to 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, NaMBT and ZMBT at manufacturing sites in the U.S. 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 data of the 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 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 (SIDS chemical) 95-16-9	2-Mercapto benzothiazole (MBT) 149-30-4	Zinc mercapto Benzothiazole (ZMBT) 155-04-4	Sodium 2-mercapto Benzothiazole (NaMBT) 2492-26-4
Hydrolysis	No data	0-15 % after 7D	No data available	Forms insoluble MBT
Biodegradation	0% after 28 D (100 mg/l) >65% after 21 D (0.8mg/l)	< 1 % after 28 D	No data available	No data available
Photodegradation	T ½ = 4.5D	T ½ = 3.2 hr (indirect) T ½ = 0.5 hr (direct)	T ½ = 1.4 hr	**T ½ = 2.8 hr**
Fugacity Level III (distribution)				
Air	2.9 %	0.507 %	**< 0.1 %**	**< 8.31 %**
Water	40.2 %	35.9 %	**14.5 %**	**85.6 %**
Soil	56.8 %	63.4 %	**66.6%**	**5.95%**
Sediment	0.122 %	0.172 %	**18.9 %**	**0.14 %**

= Non-sponsored chemical used for data purposes only

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

Ecotoxicity

Endpoint	2-Mercaptobenzothiazole (MBT) 149-30-4	Zinc mercapto Benzothiazole (ZMBT) 155-04-4	Sodium 2-mercapto Benzothiazole (NaMBT) 2492-26-4
Acute Fish Toxicity (96 hr LC50)	*P. promelas* 11 mg/l *B. rerio* 0.8 – 3.2 mg/l	*L. idus* 10-50 mg/l (48 hr)	*L. macrochirus* 3.8 mg/l *S. gairdneri* 1.8 mg/l
Acute Invertebrate Toxicity (48 hr LC50)	*Daphnia* 2.9 - 4.1 mg/l	No data available	*Daphnia* 19 mg/l
Algal Toxicity (96 hr EC50)	*S. capricornutum*. 0.25 mg/l	No data available	*S. capricornutum*. 0.3 mg/l

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

Mammalian Toxicity

Endpoint	2-Mercaptobenzothiazole (MBT) 149-30-4	Zinc mercapto Benzothiazole (ZMBT) 155-04-4	Sodium 2-mercapto Benzothiazole (NaMBT) 2492-26-4
Acute Toxicity			
Oral LD50	2830 – 3800 mg/kg bw (rat)	7500 mg/kg bw (rat)	1476-4350 mg/kg (rat) (45-50% substance content)
Dermal LD50	> 7940 mg/kg bw (rabbit)	> 7940 mg/kg bw (rabbit)	> 5010 mg/kg bw (rabbit) (45-50% substance content)
Inhalation LC50	> 1.27 mg/l (4 hrs) (rat)	No data available	> 8.2 mg/l (6 hrs) (rat) (22% substance content)
Mutagenicity			
Gene mutation	Ames = negative Yeast = negative *E. coli* = negative	Ames = negative Yeast = negative	Ames = negative Balb3T3 = negative Yeast = negative
Chromosome aberration	MLA = negative Dominant Lethal = negative MNT = negative	**OECD 475 = negative**	No data available
Repeated Dose	90 D NOAEL = 375 mg/kg bw (rat) 28 D NOAEL = 714 mg/kg (rat)	**18 month NOAEL = 1000 mg/kg bw then 2600ppm in diet (mouse)**	**90 D NOAEL = 200 mg/kg bw (rat - dermal)**
Reproductive Toxicity	NOAEL P, F1,F2= < 179 mg/kg bw Repro NOEC = 1071 mg/kg bw (rat)	No data available	No data available
Developmental Toxicity	NOAEL = 1800 – 2200 mg/kg bw (rat)	No data available	No data available

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

Endpoint	2-Mercapto benzothiazole (MBT) 149-30-4	Zinc mercapto Benzothiazole (ZMBT) 155-04-4	Sodium 2-mercapto Benzothiazole (NaMBT) 2492-26-4
Environmental Fate			
Hydrolysis	A	RA	A
Bio-degradation	A	RA	RA
Photo-degradation	A	A	A
Fugacity	A	A	A
Ecotoxicology			
Acute Fish Toxicity	A	A	A
Acute Invertebrate Toxicity	A	RA	A
Alga Toxicity	A	RA	A
Mammalian Toxicology			
Acute Toxicity	A	A	A
Mutagenicity : gene mutation	A	A	A
Mutagenicity: Chromosome aberration	A	A	RA
Repeated Dose	A	A	A
Reproductive Toxicity	A	RA	RA
Developmental Toxicity	A	RA	RA

Key for symbols in table:
A = Adequate data available
RA = Read across; Use of Category Approach
T = Testing to be done

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, and Sulfuric Acid to produce purified MBT.

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 to large industrial users as ingredients or reagents for their products or processes. Based on available information, there are no known 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 for various food-contact applications in the following sections of 21 CFR:

175.105	Components of Adhesives	MBT, ZMBT, NaMBT
176.200	Defoaming Agents, Coatings	NaMBT
176.210	Defoaming Agents, Paper	NaMBT
176.300	Slimicides	MBT
177.2600	Rubber Articles	MBT, ZMBT,
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 sophisticated industrial users handle these materials. Exposure of workers handling Benzothiazole-based thiazole materials is likely to be the greatest 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 considered 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%.