

**SCREENING-LEVEL HAZARD CHARACTERIZATION  
OF HIGH PRODUCTION VOLUME CHEMICALS**

**CHEMICAL CATEGORY NAME**  
**Benzothiazole- and Morpholine-Based Thiazoles Category**  
**5 Chemicals (See Table 1)**

The High Production Volume (HPV) Challenge Program<sup>1</sup> was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set<sup>1,2</sup>) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

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<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<sup>2</sup> U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

<sup>3</sup> U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

<p><b>Chemical Abstract Service Registry Numbers (CASRN)s</b></p>	<p><b>Sponsored Chemicals</b>  <u><b>Subcategory 1</b></u>  <u><b>Subgroup 1</b></u>  <b>149-30-4</b>  <b>2492-26-4</b>  <u><b>Subgroup 2</b></u>  <b>155-04-4</b></p> <p><u><b>Subcategory 2</b></u>  <b>95-32-9</b>  <u><b>Subgroup 3</b></u>  <b>103-34-4</b></p>
<p><b>Chemical Abstract Index Names</b></p>	<p><u><b>Subcategory 1</b></u>  <u><b>Subgroup 1</b></u>  <b>2(3H)-Benzothiazolethione</b>  <b>2(3H)-Benzothiazolethione, sodium salt</b>  <u><b>Subgroup 2</b></u>  <b>2(3H)-Benzothiazolethione, zinc salt</b></p> <p><u><b>Subcategory 2</b></u>  <u><b>Subgroup 1</b></u>  <b>Benzothiazole, 2-(4-morpholinylidithio)-</b>  <u><b>Subgroup 3</b></u>  <b>Morpholine, 4,4'-dithiobis-</b></p>
<p><b>Structural Formula</b></p>	<p><b>See Table 1</b></p>
<p style="text-align: center;"><b>Summary</b></p> <p>The benzothiazole- and morpholine based thiazoles category is divided into three subcategories defined by their structural similarities. Subcategory I, benzothiazole-based thiazoles, is composed of three compounds with benzothiazole as the main structural unit. Subcategory II, benzothiazole- and morpholine-based thiazoles, consists of one chemical that contains benzothiazole and morpholine moieties and a disulfide bond. Subcategory III, morpholine-based thiazoles, consists of one chemical that contains two morpholine moieties and a disulfide bond.</p> <p>The members of these subcategories are solids with negligible to low vapor pressures and moderate to high water solubility. The members of subcategory I are expected to have low to moderate mobility in soil. The members of subcategory II and III are expected to possess moderate to high mobility in soil. Volatilization of all compounds in this category is considered low. The rate of hydrolysis is considered negligible to slow for all compounds in the benzothiazole-based thiazoles category. The rate of atmospheric photooxidation is considered moderate to rapid for all members of the benzothiazole-based thiazoles category; however, this is not expected to be an important environmental fate process since these substances are not expected to exist in the vapor phase in the atmosphere. All of the substances in the benzothiazole- and morpholine-based thiazoles category are expected to have moderate persistence (P2) and low bioaccumulation potential (B1).</p>	

## **Human Health Hazard**

### ***Subcategory 1:***

#### ***Subgroup 1 (CASRN 149-30-4 and 2429-26-4)***

*Available data for human health effects for CASRN 149-30-4 were used to address data gaps for CASRN 2429-26-4 using a read-across approach.*

Available data for human health effects for CASRN 149-30-4 were used to address data gaps for CASRN 2429-26-4 using a read-across approach.

The acute oral and inhalation toxicity of CASRN 149-30-4 and 2429-26-4 to rats and mice is low, and the acute dermal toxicity to rabbits is low. In two separate 13-week repeated-dose toxicity (gavage) studies of CASRN 149-30-4 in rats and mice, decreased body weight gain in rats and increased mortality and decreased body weight gain in mice were seen at 750 mg/kg-day; the NOAEL for systemic toxicity for both studies is 375 mg/kg-day. In a 20-month dietary toxicity study of CASRN 149-30-4 in mice, cell infiltration in the interstitium of the kidney of male mice was seen at 58 mg/kg-bw/day; the NOAEL for systemic toxicity is 14.7 mg/kg-bw/day. In a 91-day repeated-dose dermal toxicity study of CASRN 2429-26-4 in rats, a statistically significant increase in liver weight in females was seen at 1000 mg/kg-bw/day; the NOAEL for systemic toxicity is 200 mg/kg-bw/day.

In a two-generation dietary reproductive toxicity study in rats with CASRN 149-30-4, no effects were seen on reproductive parameters; the NOAEL is 1071 mg/kg-bw/day (highest dose tested). Decreases in body weights were seen at the lowest dose of 179 mg/kg-bw/day; the NOAEL for systemic toxicity was not established. In a prenatal developmental toxicity study of CASRN 149-30-4 in rats, decreases in body weight gain and activity were observed at 1800 mg/kg-bw/day; the NOAEL for maternal toxicity is 1200 mg/kg-bw/day. No effects were seen on developmental parameters; the NOAEL for developmental toxicity is 1800 mg/kg-bw/day (highest dose tested). A prenatal developmental toxicity study in rabbits showed a NOAEL of 300 mg/kg-bw/day for maternal and developmental toxicity (highest dose tested). In the range-finding study, however, decreased body weight of dams (maternal toxicity) and decreased fetal viability and fetal body weights (developmental toxicity) were seen at 150 mg/kg-bw/day, the lowest dose tested; the NOAEL for maternal and developmental toxicity was not established. CASRN 149-30-4 was not mutagenic in bacteria or Chinese hamster ovary cells *in vitro*, but was mutagenic in mouse lymphoma cells. CASRN 2429-26-4 was not mutagenic in bacteria *in vitro*. CASRN 149-30-4 induced chromosomal aberrations in Chinese hamster ovary cells *in vitro* with metabolic activation, but did not induce micronuclei in mice bone marrow *in vivo*. CASRN 149-30-4 did not induce unscheduled DNA synthesis in rat primary hepatocytes *in vitro*. CASRN 149-30-4 was carcinogenic in rats, but not in mice. It was neurotoxic in rats. CASRN 149-30-4 is not irritating to rabbit skin; CASRN 2429-26-4 is corrosive to rabbit skin. Both CASRN 149-30-4 and CASRN 2429-26-4 are irritating to rabbit eyes. CASRN 149-30-4 is sensitizing in guinea pigs.

#### ***Subgroup 2 (CASRN 155-04-4)***

Acute oral and dermal toxicity of CASRN 155-04-4 is low in rats and rabbits, respectively. In a

repeated-dose toxicity study in which mice were administered CASRN 155-04-4 via gavage for 22 days followed by dietary administration for 18 months, no treatment-related adverse effects were observed at 1000 mg/kg-day, the only dose tested. No studies are available for reproductive and developmental toxicity. CASRN 155-04-4 was not mutagenic in bacteria *in vitro*. No studies are available for chromosomal aberrations. CASRN 155-04-4 was not carcinogenic in mice. CASRN 155-04-4 is not irritating to rabbit skin, but it is irritating to rabbit eyes. CASRN 155-04-4 is a sensitizer in mice based on local lymph node assay.

***Subcategory 2: (CASRN 95-32-9)***

CASRN 95-32-9 was not mutagenic in bacteria *in vitro*.

***Subcategory 3: (CASRN 103-34-4)***

Acute oral and acute dermal toxicity of CASRN 103-34-4 is low in rats and rabbits, respectively. In a 4-week repeated-exposure inhalation toxicity study of CASRN 103-34-4 in rats, decreases in body weights in males were observed at 0.01 mg/L/day; NOAEC is 0.001 mg/L/day. No reproductive toxicity studies were available. In a prenatal developmental toxicity study of CASRN 103-34-4 in rats, decreases in body weight in the dams, and decreases in viability, body weight, and a slight increase in the number of malformations in the fetuses were observed at 250 mg/kg-bw/day; the NOAEL for maternal and developmental toxicity is 500 mg/kg-bw/day. CASRN 103-34-4 was not mutagenic in bacteria and mouse lymphoma cells *in vitro* and did not induce chromosomal aberrations *in vivo* in rats. CASRN 103-34-4 did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro*. CASRN 103-34-4 is not irritating to rabbit skin but is irritating to rabbit eyes.

**Hazard to the Environment**

***Subcategory 1: (CASRNs 149-30-4, 2492-26-4 and 155-04-4 )***

For CASRNs 149-30-4, 2492-26-4, and 155-04-4, the 96-hour acute fish LC<sub>50</sub> values ranged from 0.73-13.3 mg/L. The acute aquatic invertebrate 48-hour EC<sub>50</sub> values for CASRNs 149-30-4, 2492-26-4, and 155-04-4 ranged from 2.9-19 mg/L. The 96-hour aquatic plant EC<sub>50</sub> values for CASRNs 149-30-4, 2492-26-4, and 155-04-4 ranged from 0.25-0.4 mg/L for biomass and 0.3 mg/L for growth. For CASRN 149-30-4, the 89-day chronic fish MATC is 0.06 mg/L. For CASRN 149-30-4, the 21-day chronic aquatic invertebrate MATC is 0.39 mg/L.

***Subcategory 2: (CASRN 95-32-9)***

The 96-hr LC<sub>50</sub> for fish was estimated by ECOSAR (v. 1.00a) to be 87.6 mg/L for CASRN 95-32-9. The 48-hr LC<sub>50</sub> for aquatic invertebrates was estimated by ECOSAR to be 8.1 mg/L for CASRN 95-32-9. For CASRN 95-32-9, the 96-hr EC<sub>50</sub> for algae was estimated by ECOSAR to be 3.0 mg/L.

***Subcategory 3: (CASRN 103-34-4)***

For CASRN 103-34-4, the 96-hour acute fish LC<sub>50</sub> value is 1.6 mg/L. The invertebrate 48-hour EC<sub>50</sub> value for CASRN 103-34-4 is 4.5 mg/L. The 96-hour aquatic plant EC<sub>50</sub> value for CASRN 103-34-4 is 29 mg/L (biomass).

***Data Gaps***

***Subcategory 1:***

***Subgroup 2 (ZMBT, CASRN 155-04-4)***

The reproductive and developmental toxicity and chromosomal aberrations endpoints were identified as data gaps under the HPV Challenge Program.

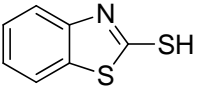
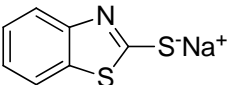
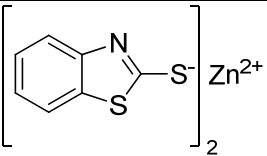
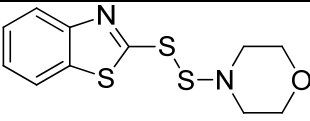
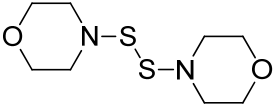
***Subcategory 2: MORFAX (CASRN 95-32-9)***

The acute toxicity to fish and aquatic invertebrates and toxicity to aquatic plants, acute oral, repeated-dose, reproductive and developmental toxicity and chromosomal aberrations endpoints were identified as data gaps under the HPV Challenge Program.

***Subcategory 3: DTDM (CASRN 103-34-4)***

Reproductive toxicity endpoint was identified as a data gap under the HPV Challenge Program.

The sponsor, American Chemistry Council (ACC) Rubber and Plastics Additives (RAPA) Panel, submitted a Test Plan and Robust Summaries to EPA for benzothiazole-based thiazoles on November 30, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on December 20, 2001 (<http://www.epa.gov/chemrtk/pubs/summaries/bnzthict/c13324tc.htm>). EPA comments on the original submission were posted to the website on September 11, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on July 17, 2003 and December 19, 2003, which were posted to the ChemRTK website on August 22, 2003 and August 31, 2004, respectively. The benzothiazole-based thiazoles category consists of the following substances:

<b>Table 1. Subcategory 1-MBT, NaMBT, ZMBT</b>			
<b>Subgroups</b>	<b>Name</b>	<b>CAS RN</b>	<b>Structure</b>
<b>Subgroup 1</b>	2-Mercaptobenzothiazole (MBT) [9th CI name: 2(3H)-Benzothiazolethione]	149-30-4	
	Sodium Mercaptobenzothiazole (NaMBT) [9th CI name: 2(3H)-Benzothiazolethione, sodium salt]	2492-26-4	
<b>Subgroup 2</b>	Zinc 2-Mercaptobenzothiazolate (ZMBT) [9th CI name: 2(3H)-Benzothiazolethione, zinc salt]	155-04-4	
<b>Subcategory 2-MORFAX</b>			
	Benzothiazole, 2-(4-morpholinyldithio)- (MORFAX) [9th CI Name: Benzothiazole, 2-(4-morpholinyldithio)-]	95-32-9	
<b>Subcategory 3-DTDM</b>			
	4,4'-Dithiodimorpholine (DTDM) [9th CI name: 4,4'-Dithiodimorpholine]	103-34-4	

### **Category Identification/Justification**

The revised test plan includes the sponsored chemicals CASRN 149-30-4 (MBT), CASRN 2492-26-4 (NaMBT), CASRN 155-04-4 (ZMBT), CASRN 95-32-9 (MORFAX) and CASRN 103-34-4 (DTDM) based on structural similarity (a benzothiazole backbone with various substitutions on the #2 carbon of the thiazole ring) and the expectation that the 2-mercaptobenzothiazole functional group will be the major determinant of the physicochemical, environmental and toxicological properties of these chemicals. The sponsor submitted revised test plans that separated the sponsored chemicals into two categories: benzothiazole-based diazoles (including MBT (CASRN 149-30-4), NaMBT (CASRN 2492-26-4) and ZMBT (CASRN 155-04-4) and benzothiazole- and morpholine-based thiazoles (including MORFAX (CASRN 95-32-9) and a new sponsored chemical, DTDM (CASRN 103-34-4). However, the sponsor did not provide adequate justification for including CASRN 155-04-4 in the same category as CASRN 149-30-4 and CASRN 2492-26-4, or for including CASRN 95-32-9 in the same category as CASRN 103-34-4. In particular, structural similarity, common precursors and common breakdown products are not in and of themselves convincing evidence that these chemicals will have similar toxicological properties for the following reasons: (1) there was insufficient evidence demonstrating that ZMBT (CASRN 155-04-4) dissociates to MBT (CASRN 149-30-4) since the zinc-sulfur bond behaves more ionically than covalently and (2) there was inadequate discussion on how MORFAX (CASRN 95-32-9) compares to other category members because the morpholinyldisulfide functional group of MORFAX (CASRN 95-32-9) may result in significantly different physicochemical, environmental and toxicological properties compared to the other category members. Therefore, for the purpose of hazard characterization, the sponsored chemicals are treated as three subcategories. Subcategory 1 is composed of three compounds with benzothiazole as the main structural unit. This subcategory is further divided into two subgroups for human health hazard: Subgroup 1 contains MBT (CASRN 149-30-4) and NaMBT (CASRN 2492-26-4) and Subgroup 2 contains ZMBT (CASRN 155-04-4). Subcategory 2 consists of one chemical, MORFAX (CASRN 95-32-9), that contains benzothiazole and morpholine moieties with a disulfide bond. Subcategory 3 consists of one chemical, DTDM (CASRN 103-34-4) that contains two morpholine moieties with a disulfide bond.

For the ecological hazard, the sponsored chemicals are also divided into three subcategories. Upon further review, EPA determined that ZMBT (CASRN 155-04-4) has similar ecotoxicological properties with MBT (CASRN 149-30-4) and NaMBT (CASRN 2492-26-4). As a result, these three sponsored chemicals should be placed into Subcategory 1 without any subgroups. Subcategory 2 and 3 contain MORFAX (CASRN 95-32-9) and DTDM (CASRN 103-34-4), respectively, for the same reasons as described above.

### **Supporting Chemicals**

In the revised test plan, data for *n*-oxydiethylene benzothiazole 2-sulfenamide (MBS, CASRN 102-77-2), benzothiazole disulfide (MBTS, CASRN 120-78-5), morpholine (CASRN 110-91-8), and benzothiazole (BTH, CASRN 95-16-9) were included as supporting chemicals for the benzothiazole- and morpholine-based thiazoles subcategories. The primary justification of using these chemicals as supporting chemicals includes structural similarity and similar physical chemical properties. MORFAX has been shown to hydrolyze to MBTS and morpholine. MBTS

has been shown to metabolize to MBT (CASRN 149-30-4). However, EPA believed that breakdown products will not necessarily pose the same hazard as the parent chemical and the sponsor did not provide any information on the duration of this process. Physical-chemical properties for the hydrolysis products/metabolites are different from the parent compounds. MORFAX is most susceptible to cleavage at the S-N bond and MBTS requires reduction rather than hydrolysis to accomplish S-S cleavage. There is insufficient evidence to justify these supporting chemicals for the subcategory. Therefore, data submitted on the proposed supporting chemicals are not included in this hazard characterization.

## **1. Chemical Identity**

### **1.1 Identification and Purity**

The following description is taken from the 2003 Test Plan and Robust Summary:

All materials in this category contain a morpholine group attached to a benzothiazole group [benzene ring + thiazole ring] or to another morpholine group via a sulfur or sulfur-sulfur bond. All category members are formed by the reaction of morpholine with benzothiazole or another molecule of morpholine in the presence of a sulfur donor. 2-Mercaptobenzothiazole and/or morpholine are the ultimate chemicals formed when these compounds undergo hydrolysis and/or metabolism. Chemicals in this category are used primarily as cure-rate accelerators or sulfur donors in natural and synthetic rubbers or as chemical intermediates in the manufacture of rubber accelerators. 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. Purity of test substances, when noted in the Robust Summary, was >95%.

### **1.2 Physical-Chemical Properties**

The physical-chemical properties of the benzothiazole-based thiazoles subcategory 1 are summarized in Table 2a, while their environmental fate properties are provided in Table 3a. The physical-chemical properties of the benzothiazole- and morpholine-based thiazoles subcategory 2 and 3 are summarized in Table 2b, while their environmental fate properties are provided in Table 3b.

### **Physical-Chemical Properties Characterization**

The benzothiazole-based thiazoles category contains solids with negligible to low vapor pressures and moderate to high water solubility.

<b>Table 2a. Physical-Chemical Properties of Subcategory 1: Benzothiazole-Based Thiazoles<sup>1</sup></b>			
<b>Property</b>	<b>2(3H)-Benzo-thiazolethione</b>	<b>2(3H)-Benzo-thiazolethione, sodium salt (1:1)</b>	<b>2(3H)-Benzothiazolethione, zinc salt (2:1)</b>
CASRN	149-30-4	2492-26-4	155-04-4
Molecular Weight	167.24	189.23	397.7
Physical State	Solid; pale, yellow monoclinic needles or leaflets <sup>2</sup>	Solid	Off-white to pale yellow solid)
Melting Point	181°C (measured)	>300 °C <sup>7</sup>	337°C (measured)
Boiling Point	>260°C (measured, decomposition)	>300°C (estimated) <sup>3</sup> Decomposes	Decomposes >362°C at 29 mm Hg (measured)
Vapor Pressure	2.2×10 <sup>-6</sup> mm Hg at 25°C (measured)	Negligible; <1x10 <sup>-8</sup> mm Hg <sup>8</sup>	Negligible; <1x10 <sup>-8</sup> mm Hg <sup>8</sup>
Water Solubility	118 mg/L at 25°C, pH = 7 (measured); 120 mg/L at 25°C (measured) <sup>4</sup>	1.3x10 <sup>5</sup> mg/L (estimated) <sup>3</sup>	90.9 mg/L at 20°C (measured)
Dissociation Constant (pK <sub>a</sub> )	6.93 (measured) <sup>5</sup>	Not applicable	Not applicable
Henry's Law Constant	4.2×10 <sup>-9</sup> atm-m <sup>3</sup> /mole (estimated) <sup>3</sup>	<1.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (estimated) <sup>3</sup>	<1.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (estimated) <sup>3</sup>
Log K <sub>ow</sub>	2.41 (measured); 2.34–2.5 at 25°C (measured)	-0.46 (measured)	5.0 (estimated) <sup>3</sup>

<sup>1</sup> Rubber and Plastic Additives Panel of the American Chemistry Council July 23, 2003. Revised Roust Summary and Test Plan for Benzothiazole-Based Thiazoles category. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/bnzthict/c13324tc.htm> as of May 05, 2010.

<sup>2</sup> Lide, D.R. 2008. CRC Handbook of Chemistry and Physics. 89<sup>th</sup> edition. CRC Press.

<sup>3</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of May 05, 2010.

<sup>4</sup> Brownlee, B.G.; Carey, J.H.; Macinnis, G.A. 1992. Aquatic environmental chemistry of z-(thiocyanomethylthio) benzothiazole and related benzothiazoles. Environ. Toxicol. Chem. 11:1153–1168.

<sup>5</sup> Serjeant, E.P.; Dempsey, B. 1979. Ionisation Constants of Organic Acids in Aqueous Solution. IUPAC Chemical Data Series No.23. Pergamon Press, New York, NY, p. 989.

<sup>6</sup> Chemicals Inspection And Testing Institute. 1992. Biodegradation And Bioaccumulation Data Of Existing Chemicals Based On The Csel Japan. Japan Chemical Industry Ecology - Toxicology And Information Center. ISBN 4-89074-101-1.

<sup>7</sup> Zhan, Ru-Fen; Chinese Journal of Chemistry 2004 V22(7) p.768-773.

<sup>8</sup> Estimated by Industrial Chemistry Branch, EPA

<b>Table 2b. Physical-Chemical Properties of Subcategory 2 and 3 Benzothiazole and Morpholine-Based Thiazoles<sup>1</sup></b>		
	<b>Subcategory 2</b>	<b>Subcategory 3</b>
<b>Property</b>	<b>Benzothiazole, 2-(4-morpholinyl)dithio-</b>	<b>Morpholine, 4,4'-dithiobis-</b>
CASRN	95-32-9	103-34-4
Molecular Weight	284.42	236.34
Physical State	Solid	White solid, crystals <sup>2</sup>
Melting Point	128.6°C (measured)	130°C (measured); 124–125°C (measured) <sup>2</sup>
Boiling Point	418.3°C (estimated)	335°C (estimated)
Vapor Pressure	1.0×10 <sup>-7</sup> mm Hg at 25°C (estimated)	2.7×10 <sup>-5</sup> mm Hg at 25°C (estimated)
Water Solubility	589 mg/L at 25°C (estimated) <sup>3</sup>	237 mg/L at 25°C (measured)
Dissociation Constant (pK <sub>a</sub> )	Not applicable	Not applicable
Henry's Law Constant	1.7×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (estimated) <sup>3</sup>	3.0×10 <sup>-10</sup> atm-m <sup>3</sup> /mole (estimated) <sup>3</sup>
Log K <sub>ow</sub>	1.59 (estimated)	2.49 (measured)

<sup>1</sup> Rubber and Plastic Additives Panel of the American Chemistry Council, July 23, 2003. Revised Robust Summary and Test Plan for Benzothiazole-Based Thiazoles category. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/bnzthict/c13324tc.htm> as of May 05, 2010.

<sup>2</sup> Lide, D.R. 2008. CRC Handbook of Chemistry and Physics. 89<sup>th</sup> edition. CRC Press.

<sup>3</sup> U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitd1.htm> as of May 05, 2010.

## **2. General Information on Exposure**

### **2.1 Production Volume and Exposure**

According to the 2006 IUR submissions, the benzothiazole- and morpholine-based Thiazole category chemicals had an aggregated production and/or import volume in the United States between 22 million pounds and 112.5 million pounds.

- CASRN 95-32-9: 500,000 to <1 million pounds;
- CASRN 149-30-4: 10 to <50 million pounds;
- CASRN 155-04-4: 500,000 to <1 million pounds;
- CASRN 2492-26-4: 10 to <50 million pounds; and
- CASRN 103-34-4: 1 to 10 million pounds.

#### CASRN 95-32-9:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include resin and synthetic rubber manufacturing as process regulators, used in vulcanization or polymerization processes. Non-confidential commercial and consumer uses of this chemical include not readily obtainable (NRO).

#### CASRN 149-30-4:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other rubber product manufacturing as process regulators, used in vulcanization or polymerization processes; rubber and plastics hoses and belting manufacturing as process regulators, used in vulcanization or polymerization processes; tire manufacturing as process regulators, used in vulcanization or polymerization processes; and other basic organic chemical manufacturing as corrosion inhibitors and anti scaling agents. Non-confidential commercial and consumer uses of this chemical include not readily obtainable (NRO).

#### CASRN 155-04-4:

Industrial processing and uses as well as commercial and consumer uses for the chemical were claimed confidential.

#### CASRN 2492-26-4:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other basic organic chemical manufacturing as corrosion inhibitors and anti-scaling agents. Non-confidential commercial and consumer uses of this chemical include not readily obtainable (NRO).

#### CASRN 103-34-4:

Non-confidential information in the IUR indicated that the industrial processing and uses of the chemical include other rubber product manufacturing as process regulators, used in vulcanization or polymerization processes and not readily obtainable (NRO); rubber and plastics hoses and belting manufacturing as process regulators, used in vulcanization or polymerization processes; tire manufacturing as process regulators, used in vulcanization or polymerization processes; and other rubber product manufacturing. Non-confidential commercial and consumer uses of this chemical include rubber and plastic products.

## 2.2 Environmental Exposure and Fate

The environmental fate properties are provided in Table 3a and 3b.

The members of subcategory I, benzothiazole-based thiazoles, are expected to have low to moderate mobility in soil. However, 2(3H)-benzothiazolethione has a  $pK_a$  of 6.93, indicating that this compound will partially exist as an anion under environmental conditions and two other substances (CASRN 155-04-4 and 2492-26-4) are salts, therefore, the mobility of these three members may be slightly higher. Only two of the members of subcategory I had experimental biodegradation data and both were shown to be not readily biodegradable. 2(3H)-benzothiazolethione was shown to be not readily biodegradable (<1% after 28 days) by an EPA OTS 796.3100 Gledhill test method listed in U.S. TSCA regulations 40 CFR 796.3100. In addition, 2(3H)-benzothiazolethione was also shown to be not readily biodegradable by only achieving 2.5% of its theoretical biochemical oxygen demand (BOD) over a 28-day period using the modified MITI test (OECD 301C). Benzothiazole, 2,2'-dithiobis- only achieved 2% in 28 days using activated sludge from industrial waste water (100 mg/L) and a manometric respirometry test indicating that the substance is not readily biodegradable. Benzothiazole, 2,2'-dithiobis- was also shown to be not readily biodegradable, only achieving 0.8% of its theoretical BOD using the modified MITI test (OECD 301C). Dissociation of 2(3H)-benzothiazolethione, sodium salt (1:1) or 2(3H)-benzothiazolethione, zinc salt (2:1) from their respective sodium and zinc cations can lead to formation of 2(3H)-benzothiazolethione and subsequently the two salts share its environmental fate characteristics. The weight of evidence from these experimental data suggests that the members of subcategory 1, benzothiazole-based thiazoles are not readily biodegradable. In subcategories 2 and 2, benzothiazole and morpholine-based thiazoles, morpholine, 4,4'-dithiobis- achieved 76% biodegradation in 46 days by using an ultimate biodegradation test measuring CO<sub>2</sub> evolution, and was classified as inherently biodegradable. A modified MITI test (OECD 301C) resulted in 2% biodegradation of morpholine, 4,4'-dithiobis- classifying it as not readily biodegradable. Based on data from both subcategories, the weight of evidence suggests that all six members of the category are not readily biodegradable, although they may be inherently biodegradable.

Volatilization of all compounds in this category is considered low given the estimated Henry's Law constants and the fact that some substances are ionic under environmental conditions. The rate of hydrolysis is considered negligible to slow for all compounds in the benzothiazole-based thiazoles category. The rate of atmospheric photooxidation is considered moderate to rapid for all members of the benzothiazole-based thiazoles category; however, this is not expected to be an important environmental fate process since these substances are not expected to exist in the vapor phase in the atmosphere. 2(3H)-benzothiazolethione has been shown to be toxic to microorganisms at 56–100 ppm and exhibit inhibitory effects at concentrations of 20–50 ppm. However, low concentrations of 2(3H)-benzothiazolethione is expected to biodegrade. Therefore, subcategory 1, benzothiazole-based thiazoles are expected to have moderate persistence (P2). A bioconcentration factor (BCF) of <0.8 was measured in *Cyprinus carpio* for 2(3H)-benzothiazolethione and 1–7.2 for benzothiazole, 2,2'-dithiobis- using the OECD 305C test for the degree of bioaccumulation. Estimated values along with experimental values indicate that subcategory I, benzothiazole-based thiazoles are expected to have a low bioaccumulation potential (B1). The members of subcategory II, benzothiazole and morpholine-based thiazoles,

are expected to have moderate persistence (P2) and low bioaccumulation potential (B1) given their estimated bioaccumulation factors.

Property	<b>2(3H)-Benzothiazolethione</b>	<b>2(3H)-Benzothiazolethione, sodium salt (1:1)</b>	<b>2(3H)-Benzothiazolethione, zinc salt (2:1)</b>
CASRN	149-30-4	2492-26-4	155-04-4
Photodegradation Half-life	3.1 hours (indirect, estimated); 0.5 hours in water and direct sunlight)	2.8 hours (estimated)	1.4 hours (estimated)
Hydrolysis Half-life	0–15% loss after 7 days at pH 7	No data	No data
Biodegradation	<1% biodegradation in 28 days (not readily biodegradable); 81% after 56 days (inherently biodegradable)	No data	No data
Bioaccumulation Factor	BCF = <0.8 (measured in carp at 0.1 mg/L) <sup>3</sup> ; BAF = 12.8 (estimated) <sup>2</sup>	BAF = 11.9 (estimated) <sup>2</sup>	BAF = 50.7 (estimated) <sup>2</sup>
Log K <sub>oc</sub>	3.1 (estimated) <sup>2</sup> ; 2.5–3.6 (measured values in various soils)	3.1 (estimated) <sup>2</sup>	4.4 (estimated) <sup>2</sup>
Fugacity (Level III Model) <sup>2</sup>			
Air (%)	<0.1	<0.1	<0.1
Water (%)	17	16.1	2.25
Soil (%)	82.1	83.1	43.5
Sediment (%)	0.8	0.8	54.2
Persistence <sup>4</sup>	P2 (moderate)	P2 (moderate)	P2 (moderate)
Bioaccumulation <sup>4</sup>	B1 (low)	B1 (low)	B1 (low)

<sup>1</sup>Rubber and Plastic Additives Panel of the American Chemistry Council, July 23, 2003. Revised Robust Summary and Test Plan for Benzothiazole-Based Thiazoles category. Available online from: <http://www.epa.gov/chemrtk/pubs/summaries/bnzthict/c13324tc.htm> as of May 05, 2010.

<sup>2</sup>U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitd.htm> as of May 05, 2010.

<sup>3</sup>National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from: [http://www.safe.nite.go.jp/english/kizon/KIZON\\_start\\_hazkizon.html](http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html) as of May 05, 2010.

<sup>4</sup>Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

Property	Benzothiazole, 2-(4-morpholinyl)dithio-	Morpholine, 4,4'-dithiobis-
CASRN	95-32-9	103-34-4
Photodegradation Half-life	22.3 hours (estimated) <sup>2</sup>	20.1 minutes (estimated) <sup>2</sup>
Hydrolysis Half-life	No data	168 hours at pH 7
Biodegradation	No data	76% in 49 days, 20.1 mg/L (measured); 2% in 28 days (not readily biodegradable) <sup>3</sup> ;
Bioaccumulation Factor	BAF = 3.2 (estimated) <sup>2</sup>	BAF = 0.9 (estimated) <sup>2</sup>
Log K <sub>oc</sub>	3.7 (estimated) <sup>2</sup>	1.6 (estimated) <sup>2</sup>
Fugacity (Level III Model) <sup>2</sup>		
Air (%)	<0.1	<0.1
Water (%)	10.8	23.3
Soil (%)	86.1	76.6
Sediment (%)	3.07	<0.1
Persistence <sup>4</sup>	P2 (moderate)	P2 (moderate)
Bioaccumulation <sup>4</sup>	B1 (low)	B1 (low)

<sup>1</sup>Rubber and Plastic Additives Panel of the American Chemistry Council, July 23, 2003. Revised Roust Summary and Test Plan for Benzothiazole-Based Thiazoles category. Available online from:

<http://www.epa.gov/chemrtk/pubs/summaries/bnzthict/c13324tc.htm> as of May 05, 2010.

<sup>2</sup>U.S. EPA. 2010. Estimation Programs Interface Suite™ for Microsoft® Windows, v4.00. U.S. Environmental Protection Agency, Washington, DC, USA. Available online from: <http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm> as of May 05, 2010.

<sup>3</sup>National Institute of Technology and Evaluation. 2002. Biodegradation and Bioaccumulation of the Existing Chemical Substances under the Chemical Substances Control Law. Available online from: [http://www.safe.nite.go.jp/english/kizon/KIZON\\_start\\_hazkizon.html](http://www.safe.nite.go.jp/english/kizon/KIZON_start_hazkizon.html) as of May 05, 2010.

<sup>4</sup>Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

**Conclusion:** The benzothiazole-based thiazoles category is divided into two subcategories defined by their structural similarities. Subcategory 1, benzothiazole-based thiazoles, is composed of four compounds with benzothiazole as the main structural unit. Two of these compounds are the sodium and zinc salts of the thiolate ion of benzothiazole. The members of both subcategory 1 and 2 and 3 are solids with negligible to low vapor pressures and moderate to high water solubilities. The members of subcategory I are expected to have low to moderate mobility in soil. The members of subcategory 2 and 3 are expected to possess moderate to high mobility in soil. Volatilization of all compounds in this category is considered low. The rate of hydrolysis is considered negligible to slow for all compounds in the benzothiazole-based thiazoles category. The rate of atmospheric photooxidation is considered moderate to rapid for all members of the benzothiazole-based thiazoles category; however, this is not expected to be an important environmental fate process since these substances are not expected to exist in the vapor phase in the atmosphere. All of the substances in the benzothiazole-based thiazoles category are expected to have moderate persistence (P2) and low bioaccumulation potential (B1).

### **3. Human Health Hazard**

A summary of health effects data submitted for SIDS endpoints is provided in Table 4. The table also indicates where data for tested category members are read-across (RA) to untested members of the category.

#### *Acute Oral Toxicity*

##### **Subcategory 1**

##### **Subgroup 1: MBT (CAS No. 149-30-4)**

(1) In two separate studies, Sprague-Dawley rats (10/sex/dose) were administered MBT via gavage (in 20% suspension in corn oil) at doses of 2000 – 6310 mg/kg. The observation period was not indicated in the robust summaries. Mortalities were observed; however, no additional details were provided.

**LD<sub>50</sub> = 2830 – 3800 mg/kg**

(2) Male mice (strain and number not specified) were administered MBT via gavage (in 0.5% carboxymethyl cellulose) at unidentified doses and observed for 72 hours following dosing.

**LD<sub>50</sub> = 2000 mg/kg**

##### **NaMBT (CAS No. 2492-26-4)**

(1) Sprague-Dawley rats (number/sex/dose not specified) were administered NaMBT via gavage. Observation period was not indicated in the robust summary. No additional details were provided.

**LD<sub>50</sub> (males) = 1615 mg/kg**

**LD<sub>50</sub> (females) = 1337 mg/kg**

**LD<sub>50</sub> (combined) = 1476 mg/kg**

(2) Sprague-Dawley rats (5/dose; 2 – 3/sex/dose) were administered undiluted NaMBT via gavage at 2510, 3160, 3980 or 5010 mg/kg and were observed for up to 14 days. Mortality mostly occurred within 2 hours of dosing at 3160 (2/5), 3980 (2/5) and 5010 (4/5) mg/kg; all deaths occurred within 1 day of dosing. No mortality occurred at 2510 mg/kg.

**LD<sub>50</sub> = 4350 mg/kg**

(3) Male rats (5/dose, strain not provided) were administered NaMBT (50% solution) via gavage at 0.625, 1.25, 2.5 and 5.0 mL/kg (equivalent to approx. 812.5, 1625, 3250 and 6500 mg/kg, respectively). Observation period was not indicated in the robust summary. Mortality was 1/5, 2/5, 3/5 and 5/5 at 0.625, 1.25, 2.5 and 5.0 mL/kg, respectively.

**LD<sub>50</sub> = 2639 mg/kg**

(4) Male rats (5/dose, strain not provided) were administered NaMBT via gavage at 312.5, 625, and 1250 mg/kg bw. Observation period was not indicated in the robust summary. Mortality was 1/5, 2/5 and 3/5 at 312.5, 625 and 1250 mg/kg, respectively.

**LD<sub>50</sub> > 625 mg/kg**

(5) Male rats (5/dose, strain not provided) were administered NaMBT via gavage at 391, 782 and 1563 mg/kg. Observation period was not indicated in the robust summary. Mortality was 1/5, 2/5 and 3/5 at 391, 782 and 1563 mg/kg, respectively.

**LD<sub>50</sub> > 782 mg/kg**

(6) Sprague-Dawley Albino rats (5/dose, 2 – 3/sex) were administered NaMBT (45 – 50% solution) via gavage at 3160, 3980, 5010 or 6310 mg/kg and observed for 14 days. Mortality was 1/5 at 3980, 2/5 at 5010 and 5/5 at 6310 mg/kg. No mortality occurred at 3160 mg/kg. (TSCATS (OTS0206761)).

**LD<sub>50</sub> = 5200 mg/kg**

(7) Sprague-Dawley Albino rats (5/dose; 2 – 3/sex) were administered NaMBT (22% solution) via oral gavage at 6310, 7940, 10,000 or 12,600 mg/kg and were observed for 14 days. Deaths occurred at 7940 (1/5), 10,000 (3/5) and 12,600 (5/5) mg/kg. No mortality occurred at 6310 mg/kg. (TSCATS (OTS0206761)).

**LD<sub>50</sub> = 9500 mg/kg**

### **Subcategory 1**

#### **Subgroup 2: ZMBT (CAS No. 155-04-4)**

(1) Sprague-Dawley rats (male and female, number/sex/dose not given) were administered ZMBT via gavage. Doses and observation period were not indicated in the robust summary.

**LD<sub>50</sub> (males) = 5735 mg/kg**

**LD<sub>50</sub> (females) = 5221 mg/kg**

**LD<sub>50</sub> (combined) = 5505 mg/kg**

(2) Sprague-Dawley rats (5/dose, 2 – 3/sex/dose) were administered ZMBT as a 20% suspension in corn oil via gavage at 5000, 6310, 7940 or 10,000 mg/kg and were observed for 14 days. Mortality occurred at 6310 (1/5), 7940 (3/5) and 10,000 (5/5) mg/kg. No deaths occurred at 5000 mg/kg.

**LD<sub>50</sub> = 7500 mg/kg**

(3) Wistar rats (10/sex) were administered ZMBT as a 33% w/v suspension in propylene glycol via gavage at 10,000 mg/kg and were observed for 14 days. Two males and two females died between 2 and 15 hours following dosing.

**LD<sub>50</sub> > 10,000 mg/kg**

#### **Subcategory 2: MORFAX (CAS NO. 95-32-9)**

No data

#### **Subcategory 3: DTDM (CAS No. 103-34-4)**

Sprague-Dawley rats (5/dose, 2 – 3/sex/dose) were administered DTDM as a 20% suspension in corn oil via gavage at 3980, 5010, 6310 or 7940 mg/kg and were observed for 14 days. Increasing mortality occurred with increasing dose at 5010 (1/5), 6310 (3/5) and 7940 (5/5) mg/kg. No deaths occurred at 3980 mg/kg.

**LD<sub>50</sub> = 5600 mg/kg**

***Acute Inhalation Toxicity***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

(1) Charles River rats (5/sex) were exposed via whole body inhalation to dry MBT as heated dust at 1270 mg/m<sup>3</sup> (~ 1.27 mg/L) for 4 hours and were observed for 14 days following dosing. No mortalities were observed. (TSCATS (OTS0206754)).

**LC<sub>50</sub> > 1.27 mg/L**

(2) Male rats (strain not specified) were exposed via whole body inhalation in glass jars to MBT vapor at a saturated vapor concentration of 104 ppm (~ 0.7 mg/L) for 7 hours. No mortalities were observed. (TSCATS (OTS0206727)).

**LC<sub>50</sub> > 0.7 mg/L**

**NaMBT (CAS No. 2492-26-4)**

(1) Six male Sprague-Dawley rats were exposed via whole body inhalation in an exposure chamber to NaMBT at 1.3 mg/L for 6 hours and were observed for 14 days following dosing. No mortalities were observed.

**LC<sub>50</sub> > 1.3 mg/L**

(2) In two separate studies, rats (strain and sex not specified) were exposed to NaMBT (22% solution in one study, substance contents not provided for the other study) at concentrations of 6.5 and 8.2 mg/L for 6 hours and observed for 14 days. No mortality was seen.

**LC<sub>50</sub> > 6.5 mg/L**

***Acute Dermal Toxicity***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

In two separate studies, three New Zealand White rabbits (two males and one female) were administered MBT (40% suspension in corn oil) via the dermal route at 5010 or 7940 mg/kg for 24 hours. The conditions were not reported. No mortalities were reported.

**LD<sub>50</sub> > 7940 mg/kg**

**NaMBT (CAS No. 2492-26-4)**

(1) Three New Zealand White rabbits (two males and one female) were administered undiluted NaMBT (50% solution) via the dermal route on to the shaved skin at 5010 (1 male) or 7940 (1 male and 1 female) mg/kg under occluded conditions for 24 hours and observed for 14 days following dosing. No mortalities were observed. (TSCATS (OTS0206761)).

**LD<sub>50</sub> > 7940 mg/kg**

(2) In three studies, rabbits (strain not specified) were administered NaMBT (22 to 50% solutions) via the dermal route at doses of 782 – 7940 mg/kg under unspecified conditions for unspecified durations. In one study that tested groups of 10 male rabbits at 782, 1563 and 3125 mg/kg, 4/10 rabbits died at 3125 mg/kg. One female rabbit died 1 day following dosing in another study. LD<sub>50</sub> values for these three studies were > 3125, > 5010 and > 7940 mg/kg. (TSCATS (OTS0206761)).

**LD<sub>50</sub> > 3125 mg/kg**

(3) Rabbits (10/dose, strain and sex not specified) were administered NaMBT (50% solution) via the dermal route at 313, 625 or 1250 mg/kg under unspecified conditions for 24 hours and observed for up to 14 days following dosing. Mortality occurred at 625 (1/10) and 1250 (4/10) mg/kg. No mortality was seen at 313 mg/kg.

**LD<sub>50</sub> > 1250 mg/kg**

**Subcategory 1**

**Subgroup 2: ZMBT (CAS No. 155-04-4)**

(1) New Zealand White rabbits (10, sex not provided) were administered ZMBT via the dermal route at 2000 mg/kg under unspecified conditions and were observed for 14 days following dosing. No mortality was observed.

**LD<sub>50</sub> > 2000 mg/kg**

(2) New Zealand White rabbits (1/sex) were administered ZMBT (40% solution) in corn oil via the dermal route at 7940 mg/kg under occluded conditions for 24 hours and were observed for 14 days following dosing. No mortality was observed.

**LD<sub>50</sub> > 7940 mg/kg**

**Subcategory 2: MORFAX (CAS NO. 95-32-9)**

No data

**Subcategory 3: DTDM (CAS No. 103-34-4)**

Four New Zealand Albino rabbits were administered DTDM via the dermal route at 3160 (1 rabbit), 5010 (1 rabbit) or 7940 (2 rabbits) mg/kg under occluded conditions for 24 hours and were observed for 14 days following dosing. One of two rabbits died at the highest dose and no mortality was seen at the lower doses.

**LD<sub>50</sub> > 5010 mg/kg**

***Repeated-Dose Toxicity***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

(1) Sprague-Dawley rats (number/sex/dose not specified) were administered MBT daily in the diet at 0, 5000, 10,000, 15,000, 20,000 or 25,000 ppm (0, approx. 57, 714, 1071, 1429 and 1786 mg/kg-bw/day, respectively) for 4 weeks. No effects were observed at 57 or 714 mg/kg-bw/day. At 1071 mg/kg-bw/day, males exhibited decreases in body weight gain and both sexes exhibited decreases in feed consumption. At 1429 and 1786 mg/kg-bw/day, both sexes demonstrated decreased body weight gain and decreased feed consumption.

**LOAEL = 1071 mg/kg-bw/day** (based on decreased weight gain in males)

**NOAEL = 714 mg/kg-bw/day**

(2) In an NTP study, Fischer 344 rats (10/sex/dose) were administered MBT via gavage at 0,188, 375, 750, 1500 or 3000 mg/kg-day for 5 days/week for 13 weeks. At 3000 mg/kg-day, all of the rats died. Due to the high mortality, the initial study was terminated and a second one was conducted using the same testing protocol with the omission of the highest dose level (3000 mg/kg-day). In the second study, no treatment-related deaths occurred. Body weight gains were lower than those in the vehicle control groups in males at 1500 mg/kg-day and in females at 750

or 1,500 mg/kg-day. Hepatomegaly occurred at 750 and 1500 mg/kg-day in males and at all doses in females; however, no microscopic pathologic changes were noted in any tissue.

[[http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch.searchhome](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchhome)]

**LOAEL = 750 mg/kg-day** (based on decreased body weight gain in females)

**NOAEL = 375 mg/kg-day**

(3) Sprague-Dawley rats (number/sex/dose not specified) were administered MBT ad libitum, in the diet at target concentrations of 0, 5000, 10,000, 15,000, 20,000 or 25,000 ppm (0, approx. 425, 839, 1232, 1696 or 2143 mg/kg-bw/day for males and 432, 874, 1320, 1703 and 2058 mg/kg-bw/day for females) for 4 weeks. Decreases in body weight gain and food consumption were observed among males and females; statistically significant at in females at 1703 and 2058 mg/kg-bw/day. Slight elevations in liver weights were observed among test animals from all dose groups.

**LOAEL = 1703 mg/kg-bw/day** (based on decreased body weight gain in females)

**NOAEL = 1320 mg/kg-bw/day**

(4) In an NTP study, B6C3F1 mice (10/sex/dose) were administered MBT daily via gavage at 0, 94, 188, 375, 750 or 1500 mg/kg-day, 5 days/week for 13 weeks. More than fifty percent of males died at 1500 mg/kg-day. Mortality among female mice was 20 and 70% at 750 and 1500 mg/kg-bw/day, respectively. Clinical signs were dose related and included lethargy in animals dosed with 375 mg/kg and lacrimation, salivation, and clonic seizure in some dosed with 750 or 1,500 mg/kg. However, there was no association between these clinical signs of toxicity and gross or microscopic pathologic effects. Males at 750 or 1500 mg/kg-bw/day exhibited a greater than 10% decrease in body weight gain. Liver/body weight ratios were elevated among high-dose animals. However, hepatomegaly was not associated with any histopathological changes (TSCATS (OTS0206747)). [[http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch.searchhome](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchhome)]

**LOAEL = 750 mg/kg-day** (based on female mortality and decreased body weight in males)

**NOAEL = 375 mg/kg-day**

(5) Slc:ddY mice (number/sex/dose not specified) were administered MBT daily in the diet at 0, 3.6, 14.7, 57.9 or 289.4 mg/kg-bw/day to males and 0, 3.6, 13.5, 58.9 or 248 mg/kg-bw/day to females for 20 months. At 289.4 mg/kg-bw/day, male mice exhibited decreases in body weight gain; and cell infiltration in the interstitium of the kidneys was observed among at 57.9 and 289.4 mg/kg-bw/day dose groups.

**LOAEL = 57.9 mg/kg-bw/day** (based cell infiltration in the interstitium of the kidney in male mice)

**NOAEL = 14.7 mg/kg-bw/day**

**NaMBT (CAS No. 2492-26-4)**

Sprague-Dawley rats (number/sex/dose not specified) were administered NaMBT via the dermal route at 0, 200, 1000 or 2000 mg/kg-bw/day for 91 days. Details of test conditions were not provided in the robust summary. Statistically significant (significance or relative/absolute weight not provided) increases in liver weights were observed in female rats at 1000 and 2000 mg/kg-bw/day. No other remarkable treatment-related effects were observed.

**LOAEL = 1000 mg/kg-bw/day** (based on increases in liver weights in female rats)

**NOAEL = 200 mg/kg-bw/day**

***Subcategory 1***

***Subgroup 2: ZMBT (CAS No. 155-04-4)***

B6C3F1 and B6AKF1 mice (18/sex) were administered ZMBT via gavage at 1000 mg/kg-day from 7 to 29 days of age followed by administration in the diet at 2600 ppm for up to 18 months. No significant treatment-related adverse effects were observed.

**LOAEL/NOAEL = Not established (one dose tested)**

***Subcategory 2: MORFAX (CAS No. 95-32-9)***

No adequate data were available.

**Subcategory 3: DTDM (CAS No. 103-34-4)**

CD rats (10/sex/dose) were administered 0, 1.1, 9.9 or 29 mg/m<sup>3</sup> DTDM (0.001, 0.01 or 0.029 mg/L, respectively) as a fine dust 6 hours/day, 5 days/week for 4 weeks (total 20 exposures). No mortality was seen. Clinical signs in the form of red discharge from the mouth and nose were limited to rats exposed to 29 mg/m<sup>3</sup>. Decreased body weights were observed in male rats at 29 mg/m<sup>3</sup> and to a lesser extent at 9.9 mg/m<sup>3</sup>. No other remarkable treatment-related effects were observed.

**LOAEC = 0.01mg/L/day** (based on decreases in body weights in male rats)

**NOAEC = 0.001 mg/L/day**

***Reproductive Toxicity***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

In a two-generation study, Sprague-Dawley rats (number/sex/dose was not given) were administered MBT ad libitum in the diet at 0, 2500, 8750 or 15,000 ppm (0, approx. 179, 625 or 1071 mg/kg-bw/day) for 10 weeks prior to mating (males and females), through gestation and lactation (females) until sacrifice. Body weights for all treated F0 males and for mid- and high-dose females were decreased in a dose-dependent manner. Body weights were also reduced in all F1 and F2 pups. The robust summary did not specify the magnitude of body weight changes observed among treated rats. At 625 and 1071 mg/kg-bw/day, F0 rats and F1 pups also exhibited decreased kidney weights, and F1 pups exhibited increased liver weights, although the robust summary did not specify if these changes were based on relative or absolute liver weights. F1 pups also demonstrated brown pigmentation in the kidneys at 625 and 1071 mg/kg-bw/day. No adverse effects were observed on reproductive parameters. The reproductive parameters assessed were not specified.

**LOAEL (systemic toxicity) = 179 mg/kg-bw/day** (based on decreased body weights)

**NOAEL (systemic toxicity) = Not established**

**NOAEL (reproductive toxicity) = 1071 mg/kg-bw/day** (highest dose tested)

**LOAEL (developmental toxicity) = 179 mg/kg-bw/day, lowest dose tested** (based on decreased body weights)

**NOAEL (developmental toxicity) = Not established**

**Subcategory 1**

**Subgroup 2: ZMBT (CAS No. 155-04-4)**

No data

**Subcategory 2: MORFAX (CAS No. 95-32-9)**

No data

**Subcategory 3: DTDM (CAS No. 103-34-4)**

No data

***Developmental Toxicity***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

(1) Pregnant Sprague-Dawley rats (number not provided) were administered MBT via gavage at 0, 300, 1200, or 1800 mg/kg-day on gestation days 6 – 15. At 1200 and 1800 mg/kg-day, rats exhibited clinical signs such as salivation, urine staining and dark red material around their mouths. At 1800 mg/kg-day, rats also exhibited decreased body weight gain and food consumption, and decreased activity. Post-implantation loss was observed at 300 and 1800 mg/kg-day rats but not at 1200 mg/kg-day. The developmental parameters assessed were not specified. Aside from post-implantation loss, there were no other indications of developmental toxicity.

**LOAEL (maternal toxicity) = 1800 mg/kg-bw/day** (based on decreased body weight gain and decreased activity)

**NOAEL (maternal toxicity) = 1200 mg/kg-bw/day**

**NOAEL (developmental toxicity) = 1800 mg/kg-bw/day (highest dose tested)**

(2) Pregnant New Zealand White rabbits (number not specified) were administered MBT via gavage at 0, 50, 150 or 300 mg/kg-day on gestation days 6 – 18. Slight reductions in maternal body weight gains (not statistically significant) were observed at 300 mg/kg-bw/day. At 300 mg/kg-day, rabbits exhibited increased liver weights. The robust summary did not specify which developmental parameters were assessed, but there were no other developmental toxic effects reported.

**NOAEL (maternal/developmental toxicity) = 300 mg/kg-bw/day** (highest dose tested)

(3) In a range-finding study, pregnant New Zealand White rabbits were administered MBT (purity not given) via gavage at 0, 150, 300, 600, 1000 or 1500 mg/kg-day on gestation days 6 – 15. Animals from 100 and 1500 mg/kg-bw/day died. Female rabbits exhibited decreases in body weight gain at 150 mg/kg-bw/day and above. Fetal viability and decreased fetal body weights were seen at 150 mg/kg-bw/day and above. MBT did not induce external abnormalities in fetuses.

**LOAEL (maternal toxicity) = 150 mg/kg-bw/day** (based on decreased body weights)

**NOAEL (maternal toxicity) = Not established**

**LOAEL (developmental toxicity) = 150 mg/kg-bw/day, lowest dose tested** (based on decreased fetal viability and decreased fetal body weights)

**NOAEL (developmental toxicity) = Not established**

**Subcategory 1**

**Subgroup 2: ZMBT (CAS No. 155-04-4)**

No data

**Subcategory 2: MORFAX (CAS No. 95-32-9)**

No data

**Subcategory 3: DTDM (CAS No. 103-34-4)**

Pregnant Charles River COBS CD rats (25/dose) were administered DTDM in corn oil via gavage at 0, 50, 250 or 500 mg/kg-day on gestation days 6–15. Four dams at 500 mg/kg-day died during the study. At 250 and 500 mg/kg-day, dams exhibited yellow staining of the ventral or anogenital haircoat, unkempt haircoat and respiratory rales. At 500 mg/kg-day, dams also exhibited decreased food consumption and a slight decrease in body weight change during gestation days 6–9 and 12–16. A higher frequency of post-implantation loss and decreased fetus viability were observed at 500 mg/kg-day compared to controls. Mean fetal body weights were also reduced at 500 mg/kg-day animals. A slight increase in the number of malformed fetuses was observed at 500 mg/kg-bw/day, but the number of litters with malformations was not significantly different than the control group.

**LOAEL (maternal toxicity) = 500 mg/kg-bw/day** (based on decreased body weights)

**NOAEL (maternal toxicity) = 250 mg/kg-bw/day**

**LOAEL (developmental toxicity) = 500 mg/kg-bw/day** (based on decreased fetal viability, decreased fetal body weights and slight increases in the number of malformed fetuses)

**NOAEL (developmental toxicity) = 250 mg/kg-bw/day**

***Genetic Toxicity – Gene Mutation***

***In vitro***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

(1) *Salmonella typhimurium* strains TA97, TA98, TA100 and TA102 were exposed to MBT at 1, 10, 100, 500, 1000 or 5000 µg/plate with and without metabolic activation. Positive and negative controls were within acceptable limits. There was a toxic response to MBT at 5000 µg/plate and in most cases at 1000 µg/plate, although the robust summary did not specify which strains did/did not exhibit a toxic response at 1000 µg/plate. There was no significant increase in the revertant colonies. MBT did not induce any mutagenic activity in any strain with or without metabolic activation.

**MBT was not mutagenic in this assay.**

(2) In two studies, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to MBT at concentrations of 1, 10, 100 and 500 µg/plate with and without metabolic activation. Positive and solvent controls responded appropriately. MBT did not induce mutagenic activity in any strain with or without metabolic activation.

**MBT was not mutagenic in this assay.**

(3) In an HGPRT assay, Chinese hamster ovary (CHO) cells were exposed to MBT at concentrations up to 333.33 µg/mL with metabolic activation and up to 33.33 µg/mL without metabolic activation. The use of positive controls was not indicated in the robust summary. The cytotoxic concentration of MBT was 1000 µg/mL with metabolic activation and 333.33 µg/mL without metabolic activation. In another HGPRT assay using V79 Chinese hamster cells, MBT was not mutagenic when tested at concentrations of 50–300 µg/mL without metabolic activation. MBT did not induce mutagenic activity with or without metabolic activation.

**MBT was not mutagenic in this assay.**

(4) In five separate studies, L5178Y mouse lymphoma cells were exposed to MBT with and without metabolic activation. Test concentrations ranged up to 150 µg/mL. Information on cytotoxicity and the use of positive controls was not provided. Results were mixed among these five studies. In two of the studies, MBT did not induce mutagenic activity with or without metabolic activation. In one study, MBT caused small increases in mutant frequency, but only at concentrations that also produced cytotoxicity. In another study, MBT induced mutagenic activity at concentrations  $\geq 5$  µg/mL with metabolic activation, but produced negative results without metabolic activation. In the final study, MBT was weakly mutagenic at cytotoxic concentration with and without metabolic activation. Based on weight of evidence, MBT is considered to be mutagenic.

**MBT was mutagenic in these assays.**

(5) *Saccharomyces cerevisiae* D4 strain was exposed to MBT at concentrations up to 500 µg/plate with and without metabolic activation. Information on cytotoxicity or the use of positive controls was not provided. MBT did not induce mutagenic activity.

**MBT was not mutagenic in this assay.**

**NaMBT (CAS No. 2492-26-4)**

In two studies, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *Saccharomyces cerevisiae* strain D4 were exposed to NaMBT at 0.001, 0.01, 0.1, 1.0 or 5.0 µL/plate with and without metabolic activation. Positive and negative controls were tested simultaneously, but results were not provided. Cytotoxicity was seen at 5 µL/plate. NaMBT did not induce any mutagenic activity in any strain with or without metabolic activation.

**NaMBT was not mutagenic in these assays.**

**Subcategory 1**

**Subgroup 2: ZMBT (CAS No. 155-04-4)**

(1) In two studies, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and *Saccharomyces cerevisiae* strain D4 were exposed to ZMBT at 0.1, 1, 10, 100 or 500 µg/plate with and without metabolic activation. Positive and negative controls were tested simultaneously, but results were not provided. Cytotoxicity was seen at 500 µg/plate for *Saccharomyces cerevisiae* and *Salmonella typhimurium* strain TA1538. ZMBT did not induce any mutagenic activity in any strain with or without metabolic activation.

**ZMBT was not mutagenic in these assays.**

(2) In two studies, *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 (only in one study) were exposed to ZMBT at concentrations up to 3000 µg/plate with and without metabolic activation. The use of positive controls and information on cytotoxicity were not provided. ZMBT was weakly positive with metabolic activation in one study and negative in the other study.

**ZMBT was mutagenic in these assays.**

**Subcategory 2: MORFAX (CAS No. 95-32-9)**

*Salmonella typhimurium* strains TA1535, TA1537, TA98 and TA100 were exposed to MORFAX (96.1% purity) at 0.1, 1.0, 10, 100 or 1000 µg/plate with and without metabolic activation. Positive and negative controls responded appropriately. Cytotoxicity was observed at 100 µg/plate. MORFAX did not induce any mutagenic activity in any strain with or without metabolic activation. (TSCATS (OTS0533561)).

**MORFAX was not mutagenic in this assay.**

**Subcategory 3: DTDM (CAS No. 103-34-4)**

(1) In two studies, *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100 and *Saccharomyces cerevisiae* strain D4 were exposed to DTDM at 0.1, 1.0, 10, 100 or 500 µg/plate with and without metabolic activation. Positive controls were tested, but results were not provided. Cytotoxicity was observed at 500 µg/plate with and without metabolic activation in the *Salmonella* strains and at 500 and 100 µg/plate, in *Saccharomyces cerevisiae*, with and without metabolic activation, respectively. DTDM did not induce any mutagenic activity in any strain with or without metabolic activation.

**DTDM was not mutagenic in these assays.**

(2) L5178Y mouse lymphoma cells were exposed to DTDM at concentrations of 0.195 – 6.25 µg/mL without metabolic activation and 0.78 – 30 µg/mL with metabolic activation. Positive controls were within acceptable limits. Cytotoxicity was observed at 1.56 µg/mL with metabolic activation and 25 µg/mL without metabolic activation. DTDM did not induce mutagenic activity in mouse lymphoma cells with or without metabolic activation.

**DTDM was not mutagenic in this assay.**

***Genetic Toxicity – Chromosomal Aberrations***

***In vitro***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

(1) Chinese hamster ovary cells were exposed to MBT at concentrations up to 500.5 µg/mL with and without metabolic activation. MBT induced chromosomal aberrations with metabolic activation at concentrations  $\geq 373.5$  µg/mL. MBT did not induce chromosomal aberrations without metabolic activation.

**MBT induced chromosomal aberrations in this assay.**

(2) In a sister chromatid exchange assay, Chinese hamster ovary cells were exposed to MBT at concentrations up to 500.5 µg/mL with and without metabolic activation. The robust summary did not provide information on cytotoxicity or on the use of positive controls in this study. MBT did not induce mutagenic activity with or without metabolic activation.

**MBT did not induce chromosomal aberrations in this assay.**

**Subcategory 1**

**Subgroup 2: ZMBT (CAS No. 155-04-4)**

No data

**Subcategory 2: MORFAX (CAS No. 95-32-9)**

No data

**Subcategory 3: DTDM (CAS No. 103-34-4)**

No data

***In vivo***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

CD-1 mice received a single i.p. injection of MBT at 300 mg/kg-bw. Details on test conditions were not provided. There was no increase in micronucleated cells when compared to control animals. MBT was not clastogenic in this assay.

**MBT did not induce micronuclei in this assay.**

**Subcategory 2: Morfax (CAS NO. 95-32-9)**

No data

**Subcategory 3: DTDM (CAS No. 103-34-4)**

Fisher 344 rats (5/sex/dose) were administered DTDM in corn oil via gavage at 2800 mg/kg-bw for 6, 18 or 30 hours. Bone marrow was sampled at 6, 24 and 48 hours following sacrifice and analyzed for cells with aberrations. During the exposure period, treated rats exhibited clinical signs such as an abnormal gait, abnormal stance, decreased body tone, arched back and discoloration on forepaws and around the nasal-oral region. DTDM did not induce structural chromosomal aberrations in rat bone marrow cells.

**DTDM did not induce chromosomal aberrations in this assay.**

***Genetic Toxicity – Other***

***In vitro***

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

Rat primary hepatocytes were exposed to MBT at unidentified concentrations under unspecified test conditions. MBT did not induce unscheduled DNA synthesis in rat hepatocytes.

**MBT did not induce unscheduled DNA synthesis in this assay.**

**Subcategory 2: Morfax (CAS NO. 95-32-9)**

No data

**Subcategory 3: DTDM (CAS No. 103-34-4)**

Fischer-344 rat hepatocytes were exposed to DTDM at 0.1, 0.5, 1, 5, 10, 50, 100, 250, 500 or 900 µg/mL in the preliminary experiment and at 1, 5, 10, 50, 100 or 250 µg/mL in the replicate experiment both with and without metabolic activation. Positive and negative controls were within acceptable limits. Cytotoxicity was observed at concentrations above 50 µg/mL. DTDM did not induce unscheduled DNA synthesis in rat hepatocytes with or without metabolic activation.

**DTDM did not induce unscheduled DNA synthesis in this assay.**

*In vivo*

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

CD-1 male rats were administered MBT at 2500, 8750 or 15,000 ppm (approx. 179, 625 or 1071 mg/kg-bw/day) in food for 13 weeks. Details on test conditions were not provided. However, MBT did not induce dominant lethality in CD-1 rat cells.

**MBT did not induce dominant lethal mutation in this assay.**

*Additional Information*

*Skin Irritation*

**Subcategory 1**

**Subgroup 1: MBT (CAS No. 149-30-4)**

(1) Six New Zealand Albino rabbits were administered undiluted MBT (98% purity, 0.35 mL in water) applied to the skin under occluded conditions for 24 hours. The average primary irritation score was 0.0. Additional details are from TSCATS (OTS0206761).

**MBT was not irritating to rabbit skin in this study.**

(2) Six New Zealand Albino rabbits were administered undiluted MBT (purity not given, 0.35 mL in water) applied to the skin under unspecified conditions for 24 hours. The average primary irritation score was 0.0. Additional details are from TSCATS (OTS0206761).

**MBT was not irritating to rabbit skin in this study.**

(3) In white rabbits, undiluted MBT was applied to the shaven intact skin of the belly for up to 10 times and to abraded skin for up to 3 times under occluded conditions. In addition, MBT as a 10% solution in Dowanol DPM was applied to the shaven intact skin of the ear or belly for up to 10 times and to abraded skin for up to 3 times under occluded conditions. The test areas were observed for healing for 1 week following treatment. Abraded skin treated with undiluted MBT exhibited very slight hyperemia. Intact skin treated with undiluted MBT exhibited slight hyperemia after each application. Intact ear skin treated with diluted MBT exhibited slight exfoliation and intact belly skin treated with diluted MBT exhibited slight hyperemia and slight to moderate exfoliation. Abraded belly skin treated with diluted MBT exhibited slight hyperemia and exfoliation. All intact skin appeared normal in 21 days and all abraded skin appeared normal in 21 days with very slight scarring. Summarized from TSCATS (OTS0206727).

**MBT was slightly irritating to rabbit skin in this study.**

**NaMBT (CAS No. 2492-26-4)**

(1) In four studies, rabbits were administered NaMBT (22 to 50%) applied to the skin. NaMBT was corrosive in all of these studies. Robust summaries for three of these studies were lacking study details including test conditions, sex and strain of test animals, duration of exposure and results data. The other robust summary detailed a study that applied undiluted NaMBT under semioclusive conditions to the shaved intact skin of six rabbits for 4 hours. NaMBT application induced cratering and injury in depth.

**NaMBT was corrosive to rabbit skin in these studies.**

(2) Rabbits were administered undiluted NaMBT (purity not given, 0.5 mL) applied to the intact and abraded shaved skin under semiocluded conditions for 24 hours. At 24 hours, necrosis and severe edema were observed. NaMBT had a severe defatting effect on rabbit skin. Skin sloughed off in 10 – 14 days and there was no injury in depth. The primary irritation score was 6.6.

**NaMBT was highly irritating to rabbit skin in this study.**

(3) New Zealand Albino rabbits were administered undiluted NaMBT (22% solution, 0.5 mL) applied to the skin for 24 hours. Skin sloughed off in 7 – 10 days and there was no deep injury to the skin. The primary irritation score was 4.9. Summarized from TSCATS (OTS0206761).

**NaMBT was moderately irritating to rabbit skin in this study.**

**Subcategory 1**

**Subgroup 2: ZMBT (CAS No. 155-04-4)**

(1) In two studies, six rabbits were administered ZMBT (0.5 g in 0.5 mL saline) applied at 50% to the skin for 24 hours. Slight dermal irritation was observed in one of three rabbits in one study. The other study did not indicate any signs of irritation.

**ZMBT was not irritating to rabbit skin in these studies.**

(2) Six Albino rabbits were administered ZMBT (0.5 g) as a finely ground powder moistened with water applied to the shaved dorsal areas under occluded conditions for 24 hours. The primary irritation score was 0.0.

**ZMBT was not irritating to rabbit skin in this study.**

**Subcategory 2: MORFAX (CAS NO. 95-32-9)**

No data

**Subcategory 3: DTDM (CAS No. 103-34-4)**

New Zealand Albino rabbits were administered undiluted DTDM (> 96% purity, 0.5 g in water) applied to shaved skin under occluded conditions for 24 hours. DTDM was not irritating to rabbit skin. The primary irritation score was 0.5.

**DTDM was not irritating to rabbit skin in this study.**

## *Eye Irritation*

### Subcategory 1

#### Subgroup 1: MBT (CAS No. 149-30-4)

(1) New Zealand Albino rabbits received undiluted MBT (98% purity) in one eye as a finely ground powder for 24 hours. The other eye was left untreated and served as a corresponding control in each animal. Test eyes were not washed. Slight to moderate erythema and moderate to copious discharge containing slight whitish exudates was observed among treated eyes at 24 hours. All irritation resolved within 72 hours. The Draize irritation score was 3.2 (slightly irritating). Additional details are from TSCATS (OTS0206761).

**MBT was slightly irritating to rabbit eyes in this study.**

(2) New Zealand Albino rabbits received MBT (purity not given) in one eye as a finely ground powder for 24 hours. The other eye was left untreated and served as a corresponding control in each animal. Test eyes were not washed. Slight to moderate erythema and discharge was observed among treated eyes at 24 hours. All irritation resolved within 48 hours. The Draize irritation score was 1.3 (not irritating). Additional details are from TSCATS (OTS0206761).

**MBT was not irritating to rabbit eyes in this study.**

(3) Rabbits received 2 drops of MBT as either an undiluted solution or as a 10% suspension in propylene glycol in each eye. The right eyes were washed within 30 seconds of treatment and the left eyes were left unwashed. Slight pain and conjunctivitis that subsided in 24 hours was observed in both eyes of rabbits treated with undiluted MBT. Moderate pain and slight conjunctivitis that subsided in 48 hours was observed in both eyes of rabbits treated with the diluted solution. Summarized from TSCATS (OTS0206727).

**MBT was slightly irritating to rabbit eyes in this study.**

#### NaMBT (CAS No. 2492-26-4)

(1) New Zealand Albino rabbits received 0.1 mL of NaMBT (22% solution) in the eye for 24 hours. The study summary did not indicate if test eyes were washed. Corneal cloudiness was observed within the first 10 minutes of treatment. Severe erythema, slight edema and copious discharge were observed beginning in the first hour of treatment and observed throughout the 24-hour exposure period. Following exposure, gradual improvement was observed and by 10 days, all irritation resolved. The average Draize irritation score was 31.4. Summarized from TSCATS (OTS0206761).

**NaMBT was highly irritating to rabbit eyes in this study.**

(2) Six Albino rabbits received undiluted NaMBT (purity not given, 0.1 mL) in one eye for 24 hours. The other eye was left untreated and served as a corresponding control in each animal. Severe erythema, moderate edema and copious discharge occurred during the first 10 minutes of treatment. Necrosis of the conjunctival sac occurred during the first hour. Gradual improvement occurred beginning at 48 hours and all irritation resolved by 7 days. The average Draize irritation score was 22.5.

**NaMBT was highly irritating to rabbit eyes in this study.**

(3) Rabbits received NaMBT (22% solution) in the eyes under unspecified test conditions for an unspecified period of time. The robust summary is lacking study details, but notes that NaMBT was moderately irritating to rabbit eyes.

**NaMBT was moderately irritating to rabbit eyes in this study.**

(4) In two studies, NaMBT (45 – 50% solution) was corrosive to rabbit eyes. In one study, discomfort, corneal opacity severe erythema, and iris showed no reaction to light, copious discharge were seen in 10 minutes. After 24 hours observation, the test substance was considered to be corrosive. TSCATS (OTS0206761).

**NaMBT was corrosive to rabbit eyes in these studies.**

#### Subcategory 1

##### Subgroup 2: ZMBT (CAS No. 155-04-4)

(1) Six rabbits received ZMBT at 74.06% in the eyes for 24 hours. Study details were not provided. ZMBT caused conjunctival redness, chemosis and discharge in treated eyes.

**ZMBT was slightly irritating to rabbit eyes in this study.**

(2) Six rabbits received ZMBT (100 mg) as a finely ground powder in the conjunctival sac of one eye for 24 hours. The other eye was left untreated and served as a corresponding control in each animal. Test eyes were not rinsed. Initial irritation was noted, but the mean irritation score decreased over time and at 72 hours, all irritation had subsided.

**ZMBT was slightly irritating to rabbit eyes in this study.**

##### Subcategory 2: Morfax (CAS NO. 95-32-9)

No data

##### Subcategory 3: DTDM (CAS No. 103-34-4)

New Zealand Albino rabbits received undiluted DTDM (> 96% purity, 100 mg) as a finely ground powder in one eye for 24 hours. The other eye was left untreated and served as a corresponding control in each animal. Rabbits indicated slight discomfort in test eyes immediately. Moderate erythema, slight edema and copious discharge were observed at 1 hour. At 24 hours, moderate to severe erythema, very slight edema and copious discharge containing whitish exudates was observed. Gradual improvement was observed at 48 hours and by 168 hours, all animals received an irritation score of 0.0.

**DTDM was irritating to rabbit eyes in this study.**

## *Sensitization*

### *Subcategory 1*

#### *Subgroup 1: MBT (CAS No. 149-30-4)*

(1) Guinea pigs were challenged with MBT (98% purity). Study details were not provided. MBT was classified as a sensitizing agent in the maximization test.

**MBT was sensitizing to guinea pigs in this study.**

(2) Guinea pigs were challenged with MBT in petrolatum at 0.1, 0.5 or 2%. None of the guinea pigs treated with 0.1% MBT exhibited signs of a reaction. Twenty percent of the guinea pigs treated with 0.5%, and 70% of the guinea pigs treated with 2% exhibited signs of reaction to MBT. Details on the types of reactions observed and overall study details were not provided.

**MBT was sensitizing to guinea pigs in this study.**

(3) Five additional studies based on the guinea pig maximization test were included in the robust summaries for evaluating sensitization to MBT. These summaries were lacking study details including test conditions and results data. However, each of the five studies classified MBT as a sensitizing agent.

**MBT was sensitizing to guinea pigs in these studies.**

(4) Three studies based on the mouse local lymph node assay were included in the robust summaries for evaluating sensitization to MBT. These summaries were lacking study details including test conditions and results. However, each of the three studies classified MBT as a sensitizing agent.

**MBT was sensitizing to mouse lymph nodes in these studies.**

### *Subcategory 1*

#### *Subgroup 2: ZMBT (CAS No. 155-04-4)*

(1) ZMBT was tested as a sensitizing agent in a mouse local lymph node assay. Study design details were not provided. The effective concentration inducing a 3-fold increase in 3H-thymidine incorporation in the harvested lymph cells was 30.3% indicating a weak response.

**ZMBT was weakly sensitizing to mouse lymph nodes in this study.**

(2) Ten guinea pigs were challenged with ZMBT (0.5 g in 0.5 mL saline) in a guinea pig maximization test. Study details were not provided. No signs of sensitization were noted in the test animals.

**ZMBT was not sensitizing to guinea pigs in this study.**

#### *Subcategory 2: MORFAX (CAS NO. 95-32-9)*

No data

## *Carcinogenicity*

### *Subcategory 1*

#### *Subgroup 1: MBT (CAS No. 149-30-4)*

(1) In an NTP study, Fischer 344 rats were administered MBT (98% purity) at 0, 375 or 750 mg/kg-bw for males and at 0, 188 or 375 mg/kg-bw for females via gavage 5 days/week for 2 years. No effects were noted in low-dose females. Under the conditions of these 2-year gavage

studies, there was some evidence of carcinogenic activity of MBT for male F344/N rats, indicated by increased incidences of mononuclear cell leukemia, pancreatic acinar cell adenomas, adrenal gland pheochromocytomas, and preputial gland adenomas or carcinomas (combined). There was some evidence of carcinogenic activity for female F344/N rats, indicated by increased incidences of adrenal gland pheochromocytomas and pituitary gland adenomas. [[http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch.searchhome](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchhome)]

**MBT was carcinogenic in this study.**

(2) In an NTP study, B6C3F1 mice were administered MBT (98% purity) at 0, 375 or 750 mg/kg-bw in the diet 5 days/week for 2 years. There was no evidence of carcinogenic activity of MBT for male B6C3F1 mice dosed with 375 or 750 mg/kg. There was equivocal evidence of carcinogenic activity for female B6C3F1 mice, indicated by increased incidences of hepatocellular adenomas or carcinomas (combined). [[http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch.searchhome](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchhome)]

**MBT was not carcinogenic in this study.**

(3) Slc:ddY mice were administered technical-grade MBT at 0, 3.6, 14.7, 57.9 or 289.4 mg/kg-bw/day in males and at 0, 3.6, 13.5, 58.9 or 284 mg/kg-bw/day in females continuously in the diet for 20 months. MBT did not induce a significant increase in the frequency of tumors in treated mice.

**MBT was not carcinogenic in this study.**

(4) Hybrid mice (C57BL/6xC3H/Anf or C57BL/6xAKR) (18/sex/dose) were administered MBT (purity not given) in 0.5% gelatin at 100 mg/kg-bw/day via gavage for 3 weeks and subsequently at 50 mg/kg-bw/day in the diet for 17 months. MBT did not induce a significant increase in the frequency of tumors in treated mice.

**MBT was not carcinogenic in this study.**

### **Subcategory 1**

#### **Subgroup 2: ZMBT (CAS No. 155-04-4)**

As described previously under Repeated-Dose Toxicity, B6C3F1 and B6AKF1 mice (18/sex) were administered ZMBT (purity not given) via gavage at 1000 mg/kg-bw/day from 7 to 29 days of age followed by administration in the diet thereafter for up to 18 months. There were no statistically significant increases in tumor incidences observed.

**ZMBT was not carcinogenic in this study.**

### ***Neurotoxicity***

#### **Subcategory 1**

##### **Subgroup 1: MBT (CAS No. 149-30-4)**

(1) Sprague-Dawley rats were administered a single dose of MBT (purity not given) via gavage in corn oil at 0 or 2750 mg/kg-bw and were observed for 24 hours for effects on motor activity. Decreased motor activity was noted.

**MBT was neurotoxic in this study.**

(2) Sprague-Dawley rats were administered a single dose of MBT (purity not given) via gavage in corn oil at 0, 500, 1250 or 2750 mg/kg-bw and were observed for 14 days. Functional observational battery and motor activity assessment were performed. The robust summary did

not specify the findings, but indicated that the effects that were observed may have been related to an acute, non-specific toxicity without apparent neurotoxicity.

**MBT was not neurotoxic in this study.**

**Conclusion:**

***Subcategory 1:***

***Subgroup 1 (CASRN 149-30-4 and 2429-26-4)***

*Available data for human health effects for CASRN 149-30-4 were used to address data gaps for CASRN 2429-26-4 using a read-across approach.*

Available data for human health effects for CASRN 149-30-4 were used to address data gaps for CASRN 2429-26-4 using a read-across approach.

The acute oral and inhalation toxicity of CASRN 149-30-4 and 2429-26-4 to rats and mice is low, and the acute dermal toxicity to rabbits is low. In two separate 13-week repeated-dose toxicity (gavage) studies of CASRN 149-30-4 in rats and mice, decreased body weight gain in rats and increased mortality and decreased body weight gain in mice were seen at 750 mg/kg-day; the NOAEL for systemic toxicity for both studies is 375 mg/kg-day. In a 20-month dietary toxicity study of CASRN 149-30-4 in mice, cell infiltration in the interstitium of the kidney of male mice was seen at 58 mg/kg-bw/day; the NOAEL for systemic toxicity is 14.7 mg/kg-bw/day. In a 91-day repeated-dose dermal toxicity study of CASRN 2429-26-4 in rats, a statistically significant increase in liver weight in females was seen at 1000 mg/kg-bw/day; the NOAEL for systemic toxicity is 200 mg/kg-bw/day.

In a two-generation dietary reproductive toxicity study in rats with CASRN 149-30-4, no effects were seen on reproductive parameters; the NOAEL is 1071 mg/kg-bw/day (highest dose tested). Decreases in body weights were seen at the lowest dose of 179 mg/kg-bw/day; the NOAEL for systemic toxicity was not established. In a prenatal developmental toxicity study of CASRN 149-30-4 in rats, decreases in body weight gain and activity were observed at 1800 mg/kg-bw/day; the NOAEL for maternal toxicity is 1200 mg/kg-bw/day. No effects were seen on developmental parameters; the NOAEL for developmental toxicity is 1800 mg/kg-bw/day (highest dose tested). A prenatal developmental toxicity study in rabbits showed a NOAEL of 300 mg/kg-bw/day for maternal and developmental toxicity (highest dose tested). In the range-finding study, however, decreased body weight of dams (maternal toxicity) and decreased fetal viability and fetal body weights (developmental toxicity) were seen at 150 mg/kg-bw/day, the lowest dose tested; the NOAEL for maternal and developmental toxicity was not established. CASRN 149-30-4 was not mutagenic in bacteria or Chinese hamster ovary cells *in vitro*, but was mutagenic in mouse lymphoma cells. CASRN 2429-26-4 was not mutagenic in bacteria *in vitro*. CASRN 149-30-4 induced chromosomal aberrations in Chinese hamster ovary cells *in vitro* with metabolic activation, but did not induce micronuclei in mice bone marrow *in vivo*. CASRN 149-30-4 did not induce unscheduled DNA synthesis in rat primary hepatocytes *in vitro*. CASRN 149-30-4 was carcinogenic in rats, but not in mice. It was neurotoxic in rats. CASRN 149-30-4 is not irritating to rabbit skin; CASRN 2429-26-4 is corrosive to rabbit skin. Both CASRN 149-30-4 and CASRN 2429-26-4 are irritating to rabbit eyes. CASRN 149-30-4 is sensitizing in guinea pigs.

***Subgroup 2 (CASRN 155-04-4)***

Acute oral and dermal toxicity of CASRN 155-04-4 is low in rats and rabbits, respectively. In a repeated-dose toxicity study in which mice were administered CASRN 155-04-4 via gavage for

22 days followed by dietary administration for 18 months, no treatment-related adverse effects were observed at 1000 mg/kg-day, the only dose tested. No studies are available for reproductive and developmental toxicity. CASRN 155-04-4 was not mutagenic in bacteria *in vitro*. No studies are available for chromosomal aberrations. CASRN 155-04-4 was not carcinogenic in mice. CASRN 155-04-4 is not irritating to rabbit skin, but it is irritating to rabbit eyes. CASRN 155-04-4 is a sensitizer in mice based on local lymph node assay.

***Subcategory 2: (CASRN 95-32-9)***

CASRN 95-32-9 was not mutagenic in bacteria *in vitro*.

***Subcategory 3: (CASRN 103-34-4)***

Acute oral and acute dermal toxicity of CASRN 103-34-4 is low in rats and rabbits, respectively. In a 4-week repeated-exposure inhalation toxicity study of CASRN 103-34-4 in rats, decreases in body weights in males were observed at 0.01 mg/L/day; NOAEC is 0.001 mg/L/day. No reproductive toxicity studies were available. In a prenatal developmental toxicity study of CASRN 103-34-4 in rats, decreases in body weight in the dams, and decreases in viability, body weight, and a slight increase in the number of malformations in the fetuses were observed at 250 mg/kg-bw/day; the NOAEL for maternal and developmental toxicity is 500 mg/kg-bw/day. CASRN 103-34-4 was not mutagenic in bacteria and mouse lymphoma cells *in vitro* and did not induce chromosomal aberrations *in vivo* in rats. CASRN 103-34-4 did not induce unscheduled DNA synthesis in rat hepatocytes *in vitro*. CASRN 103-34-4 is not irritating to rabbit skin but is irritating to rabbit eyes.

<b>Table 4. Summary of Human Health Data</b>					
<b>Endpoints</b>	<b>Subcategory 1</b>			<b>Subcategory 2</b>	<b>Subcategory 3</b>
	<b>Subgroup 1</b>		<b>Subgroup 2</b>		
	<b>MBT (149-30-4)</b>	<b>NaMBT (2492-26-4)</b>	<b>ZMBT (155-04-4)</b>	<b>MORFAX (95-32-9)</b>	<b>DTDM (103-34-4)</b>
<b>Acute Oral Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>2000</b>	<b>1337</b>	<b>&gt; 5000</b>	No Data	<b>5600</b>
<b>Acute Inhalation Toxicity LC<sub>50</sub> (mg/L)</b>	<b>&gt; 0.7</b>	<b>&gt; 1.3</b>	–	–	–
<b>Acute Dermal Toxicity LD<sub>50</sub> (mg/kg-bw)</b>	<b>&gt; 7940</b>	<b>&gt; 1250</b>	<b>&gt; 2000</b>	–	<b>&gt; 5010</b>
<b>Repeated-Dose Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)</b>	(Mice, diet) NOAEL = 14.7 LOAEL = 58.9  (Rat, gavage) NOAEL = 375 LOAEL = 750	No Data (Mice, diet) NOAEL = 14.7 LOAEL = 58.9  (Rat, gavage) NOAEL = 375 LOAEL = 750 (RA)	<b>1000 (only dose tested)</b>	No data	–
<b>Repeated-Dose Toxicity NOAEL/LOAEL Inhalation (mg/L/day)</b>	–	–	–	–	<b>NOAEC = 0.001 LOAEC = 0.01</b>
<b>Repeated-Dose Toxicity NOAEL/LOAEL Dermal (mg/kg-bw/day)</b>	No Data NOAEL = 200 LOAEL = 1000 (RA)	<b>NOAEL = 200 LOAEL = 1000</b>	–	–	–
<b>Reproductive Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day) Systemic Toxicity</b>	NOAEL = NE LOAEL = 179  NOAEL = 1071 (hdt)	No Data NOAEL = NE LOAEL = 179  NOAEL = 1071 (hdt) (RA)	No data	No data	–
<b>Reproductive Toxicity NOAEL/LOAEL Inhalation (mg/L/day)</b>	–	–	–	–	No data
<b>Developmental Toxicity NOAEL/LOAEL Oral (mg/kg-bw/day)</b>	(Rat) NOAEL = 1200 LOAEL = 1800  NOAEL = 1800 (hdt)	No Data (Rat) NOAEL = 1200 LOAEL = 1800  NOAEL = 1800 (hdt)	No data	No data	<b>NOAEL = 250 LOAEL = 500  NOAEL = 250 LOAEL = 500</b>

<b>Table 4. Summary of Human Health Data</b>					
<b>Endpoints</b>	<b>Subcategory 1</b>			<b>Subcategory 2</b>	<b>Subcategory 3</b>
	<b>Subgroup 1</b>		<b>Subgroup 2</b>		
	<b>MBT (149-30-4)</b>	<b>NaMBT (2492-26-4)</b>	<b>ZMBT (155-04-4)</b>	<b>MORFAX (95-32-9)</b>	<b>DTDM (103-34-4)</b>
<b>Maternal Toxicity</b> <b>Developmental Toxicity</b>	<b>(Rabbit)</b> NOAEL = NE LOAEL = 150  NOAEL = NE LOAEL = 150	No Data (Rabbit) NOAEL = NE LOAEL = 150  NOAEL = NE LOAEL = 150 (RA)			
<b>Genetic Toxicity – Gene Mutation <i>In vitro</i></b>	<b>Negative</b>	<b>Negative</b>	<b>Negative Weakly positive</b>	<b>Negative</b>	<b>Negative</b>
<b>Genetic Toxicity – Chromosomal Aberrations <i>In vitro</i></b>	<b>Positive</b>	No Data Positive (RA)	No data	No data	–
<b>Genetic Toxicity – Chromosomal Aberrations <i>In vivo</i></b>	<b>Negative</b>	No Data Negative (RA)	–	–	<b>Negative</b>
<b>Genetic Toxicity – Other <i>In vitro</i> Unscheduled DNA synthesis</b>	<b>Negative</b>	No Data Negative (RA)	–	–	<b>Negative</b>
<b>Genetic Toxicity – Other <i>In vivo</i> Dominant Lethal Mutation</b>	<b>Negative</b>	No Data Negative (RA)	–	–	–

Table 4. Summary of Human Health Data					
Endpoints	Subcategory 1			Subcategory 2	Subcategory 3
	Subgroup 1		Subgroup 2		
	MBT (149-30-4)	NaMBT (2492-26-4)	ZMBT (155-04-4)	MORFAX (95-32-9)	DTDM (103-34-4)
<b>Additional Information</b>					
<b>Skin Irritation</b>	<b>Irritating</b>	<b>Irritating, corrosive</b>	<b>Not irritating</b>	–	<b>Irritating</b>
<b>Eye Irritation</b>	<b>Irritating</b>	<b>Irritating, corrosive</b>	<b>Irritating</b>	–	<b>Irritating</b>
<b>Sensitization</b>	<b>Sensitizing (Guinea pig)</b>	No Data Sensitizing (RA)	–	–	<b>Not sensitizing</b>
<b>Carcinogenicity</b>	<b>(Rat) Positive</b>	No Data <b>(Rat) Positive</b>	<b>Negative</b>	–	–
<b>Neurotoxicity</b>	<b>(Mice) Negative</b>	<b>(Mice) Negative</b>	–	–	–
	<b>Positive</b>			–	–

Measured data in bold text; (RA) = Read Across; – indicates that endpoint was not evaluated for this substance; hdt = highest dose tested

#### **4. Hazard to the Environment**

A summary of aquatic toxicity data submitted for SIDS endpoints is provided in Table 5.

##### **Acute Toxicity to Fish**

###### ***Subcategory 1: (CASRN 149-30-4, 2492-26-4 and 155-04-4)***

###### ***MBT (CASRN 149-30-4)***

(1) Fathead minnows (*Pimephales promelas*) were exposed to MBT (99% purity) at nominal concentrations of 0, 4.2, 7.5, 14, 24, 42 or 75 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 11 mg/L**

(2) Bluegill sunfish (*Lepomis macrochirus*) were exposed to MBT (purity not given) at nominal concentrations of 0, 0 (vehicle control), 0.75, 1, 1.4, 1.8, 2.4, 3.2 or 5.6 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 1.5 mg/L**

(3) Rainbow trout (*Oncorhynchus mykiss*) were exposed to MBT (purity not given) at nominal concentrations of 0, 0 (vehicle control), 0.42, 0.56, 0.75, 1 or 1.8 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 0.75 mg/L**

(4) Rainbow trout (*Oncorhynchus mykiss*) were exposed to MBT (purity not given) at measured concentrations of 0, <0.01, 0.1, 0.29, 0.79 or 1.65 mg/L under flow-through conditions for up to 8 days.

**48-h LC<sub>50</sub> = 0.73 mg/L**

###### ***NaMBT (CASRN 2492-26-4)***

(1) Bluegill sunfish (*Lepomis macrochirus*) were exposed to NaMBT (50% solution) in acetone at nominal concentrations of 0, 2.1, 2.8, 3.2, 3.7, 4.9, 6.5 or 10 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 3.8 mg/L**

(2) Rainbow trout (*Salmo gairdneri*) were exposed to NaMBT (50% solution) in acetone at nominal concentrations of 0, 1.0, 1.4, 1.8, 2.4 or 3.2 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 1.8 mg/L**

(3) Bluegill sunfish (*Lepomis macrochirus*) were exposed to NaMBT (50% solution) at nominal concentrations of 0, 9.5, 12 or 15 mg/L under static conditions for 96 hours. No fish from the lowest exposure group died. Most of the fish that died in the 12 and 15 mg/L groups died during the first 24 hours following exposure.

**96-h LC<sub>50</sub> = 13.3 mg/L**

(4) Rainbow trout (*Oncorhynchus mykiss*) were exposed to NaMBT (50% solution) at nominal concentrations of 0, 1.99, 2.58 or 3.16 mg/L under static conditions for 96 hours. No fish from the lowest exposure group died. Mortality in the 2.58 and 3.16 mg/L exposure groups occurred during the first 24 hours following exposure.

**96-h LC<sub>50</sub> = 2.88 mg/L**

**ZMBT (CASRN 155-04-4)**

The toxicity of CASRN 155-04-4 was calculated at 1.59 ppm based on a molecular weight adjustment from the toxicity of zinc.

**Subcategory 2: (CASRN 95-32-9)**

**MORFAX (CASRN 95-32-9)**

A 96-hour LC<sub>50</sub> for fish estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 95-32-9.

**96-hr LC<sub>50</sub> = 87.6 mg/L (estimated)**

**Subcategory 3 (CASRN 103-34-4)**

**DTDM (CASRN 103-34-4)**

(1) Rainbow trout (*Salmo gairdneri*) were exposed to DTDM (> 96% purity) in acetone at nominal concentrations of 0, 1.0, 1.4, 1.8, 2.4, 3.2, 4.2 or 5.6 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 1.8 mg/L**

(2) Bluegill sunfish (*Lepomis macrochirus*) were exposed to DTDM (> 96% purity) in acetone at nominal concentrations of 0, 0.75, 1.0, 1.4, 1.8, 2.4, 3.2, 4.2 or 5.6 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 1.6 mg/L**

(3) Fathead minnows (*Pimephales promelas*) were exposed to DTDM (> 96% purity) in acetone at nominal concentrations of 0, 1.0, 1.8, 3.2, 5.6 or 10 mg/L under static conditions for 96 hours.

**96-h LC<sub>50</sub> = 3.5 mg/L**

(4) Rainbow trout (*Oncorhynchus mykiss*) were exposed to DTDM (> 96% purity) in acetone at measured concentrations of 0, 0.33, 0.73, 1.24, 2.7 or 5.03 mg/L under flow-through conditions for up to 168 hours.

**96-h LC<sub>50</sub> = 3.68 mg/L**

### **Acute Toxicity to Aquatic Invertebrates**

#### ***Subcategory 1: (CASRN 149-30-4, 2492-26-4 and 155-04-4)***

##### ***MBT (CASRN 149-30-4)***

(1) Water fleas (*Daphnia magna*) were exposed to MBT (100% purity) at measured concentrations of 0, 1.2, 1.9, 3.2, 5.1 or 8.5 mg/L under static conditions for 48 hours.

**48-h EC<sub>50</sub> = 2.9 mg/L**

(2) Water fleas (*Daphnia magna*) were exposed to MBT (98% purity) in acetone at nominal concentrations of 0, 1.0, 1.8, 3.2, 5.6 or 10.0 mg/L under static conditions for 48 hours. A solvent control using acetone was also tested.

**48-h EC<sub>50</sub> = 4.1 mg/L**

##### ***NaMBT (CASRN 2492-26-4)***

Water fleas (*Daphnia magna*) were exposed to NaMBT (50% solution) in acetone at nominal concentrations of 10, 18, 32, 56 or 100 mg/L under static conditions for 48 hours. A solvent control using acetone was also tested.

**48-h EC<sub>50</sub> = 19 mg/L**

##### ***ZMBT (CASRN 155-04-4)***

The toxicity of CASRN 155-04-4 was calculated at 1.59 ppm based on a molecular weight adjustment from the toxicity of zinc.

#### ***Subcategory 2: (CASRN 95-32-9)***

##### ***MORFAX (CASRN 95-32-9)***

A 48-hour EC<sub>50</sub> for *Daphnia* estimated by ECOSAR v1.00a was used to evaluate the acute toxicity of CASRN 95-32-9.

**48-hr EC<sub>50</sub> = 8.1 mg/L (estimated)**

#### ***Subcategory 3 (CASRN 103-34-4)***

##### ***DTDM (CASRN 103-34-4)***

Water fleas (*Daphnia magna*) were exposed to DTDM (purity > 96%) in acetone at nominal concentrations of 0, 1, 1.8, 5.6, 10 or 32 mg/L under static conditions for 48 hours.

**48-h EC<sub>50</sub> = 4.5 mg/L**

### **Toxicity to Aquatic Plants**

#### ***Subcategory 1: (CASRN 149-30-4, 2492-26-4 and 155-04-4)***

##### ***MBT (CASRN 149-30-4)***

Green algae (*Pseudokirchneriella subcapitata*) were exposed to MBT (purity not given) at nominal concentrations of 0, 0.03, 0.06, 0.1, 0.3 or 0.6 mg/L for 96 hours. *In vivo* chlorophyll 96-hour EC<sub>50</sub> was 0.23 mg/L.

**96-h EC<sub>50</sub> (biomass) = 0.25 mg/L**

##### ***NaMBT (CASRN 2492-26-4)***

Green algae (*Pseudokirchneriella subcapitata*) were exposed to NaMBT (50% solution) at nominal concentrations of 0, 0.3, 0.6, 1, 3 or 6 mg/L for 96 hours.

**96-h EC<sub>50</sub> (biomass) = 0.4 mg/L**

**96-h EC<sub>50</sub> (growth) = 0.3 mg/L**

##### ***ZMBT (CASRN 155-04-4)***

The toxicity of CASRN 155-04-4 was calculated at 1.59 ppm based on a molecular weight adjustment from the toxicity of zinc.

#### ***Subcategory 2: (CASRN 95-32-9)***

##### ***MORFAX (CASRN 95-32-9)***

A 96-hour EC<sub>50</sub> for algae estimated by ECOSAR v1.00a was used to evaluate the aquatic toxicity of CASRN 95-32-9.

**96-hr EC<sub>50</sub> = 3.0 mg/L (estimated)**

#### ***Subcategory 3 (DTDM, CASRN 103-34-4)***

Green algae (*Pseudokirchneriella subcapitata*) were exposed to DTDM (> 96% purity) in acetone at nominal concentrations of 0, 10, 18, 32, 56 or 100 mg/L for 96 hours. The EC<sub>50</sub> value based on chlorophyll a was 29 mg/L.

**96-h EC<sub>50</sub> (biomass) = 29 mg/L**

### **Chronic Toxicity to Fish**

#### ***Subcategory 1: (CASRN 149-30-4, 2492-26-4 and 155-04-4)***

##### ***MBT (CASRN 149-30-4)***

Rainbow trout (*Oncorhynchus mykiss*) were exposed to MBT (98.2% purity) at measured concentrations of 0, 0.021, 0.041, 0.078, 0.16, or 0.32 mg a.i./L. There was no effect on embryo viability or survival. Maximum acceptable toxicity concentration was established for larval length. The no-observed-effect level was 0.041 mg a.i./L and the lowest-observed-effect level was 0.078 mg a.i./L. The maximum acceptable toxicant concentration was 0.057 mg/L.

**NOAEC = 0.041 mg a.i./L (based on growth)**

**LOAEC = 0.078 mg a.i./L**

**MATC (growth) = 0.057 mg/L**

### **Chronic Toxicity to Invertebrates**

#### ***Subcategory 1: (CASRN 149-30-4, 2492-26-4 and 155-04-4)***

##### ***MBT (CASRN 149-30-4)***

(1) Water fleas (*Daphnia magna*) were exposed to MBT (98.2% purity) at nominal concentrations of 0, 0.029, 0.055, 0.12, 0.24 or 0.47 mg a.i./L for 21 days. The maximum acceptable toxicant concentration was 0.34 mg/L.

**NOAEC = 0.24 mg/L**

**LOAEC = 0.47 mg a.i./L**

**MATC (reproduction) = 0.34 mg/L**

(2) Water fleas (*Daphnia magna*) were exposed to MBT (99.4% purity) at nominal concentrations of 0.07, 0.22, 0.7, 2.22 or 7 mg/L for 21 days. The maximum acceptable toxicant concentration was 0.34 mg/L.

**NOAEC = 0.22 mg/L (based on reproduction)**

**LOAEC = 0.7 mg/L**

**MATC (reproduction) = 0.39 mg/L**

#### **Conclusion:**

#### ***Subcategory 1: (CASRN 149-30-4, 2492-26-4 and 155-04-4)***

For CASRN 149-30-4, 2492-26-4, and 155-04-4, the 96-hour acute fish LC<sub>50</sub> values ranged from 0.73-13.3 mg/L. The acute aquatic invertebrate 48-hour EC<sub>50</sub> values for CASRN 149-30-4, 2492-26-4, and 155-04-4 ranged from 2.9-19 mg/L. The 96-hour aquatic plant EC<sub>50</sub> values for CASRN 149-30-4, 2492-26-4, and 155-04-4 ranged from 0.25-0.4 mg/L for biomass and is 0.3 mg/L for growth. For CASRN 149-30-4, the 89-day chronic fish MATC is 0.06 mg/L. For CASRN 149-30-4, the 21-day chronic aquatic invertebrate MATC is 0.39 mg/L.

#### ***Subcategory 2: (CASRN 95-32-9)***

The 96-hr LC<sub>50</sub> for fish was estimated by ECOSAR (v. 1.00a) to be 87.6 mg/L for CASRN 95-32-9. The 48-hr LC<sub>50</sub> for aquatic invertebrates was estimated by ECOSAR to be 8.1 mg/L for CASRN 95-32-9. For CASRN 95-32-9, the 96-hr EC<sub>50</sub> for algae was estimated by ECOSAR to be 3.0 mg/L.

#### ***Subcategory 3 (CASRN 103-34-4)***

For CASRN 103-34-4, the 96-hour acute fish LC<sub>50</sub> value is 1.6 mg/L. The invertebrate 48-hour EC<sub>50</sub> value for CASRN 103-34-4 is 4.5 mg/L. The 96-hour aquatic plant EC<sub>50</sub> value for CASRN 103-34-4 is 29 mg/L (biomass).

**Table 5. Summary of Environmental Effects – Aquatic Toxicity Data**

Endpoints	Subcategory 1			Subcategory 2	Subcategory 3
	MBT (CASRN 149-30-4)	NaMBT (CASRN 2492-26-4)	ZMBT (CASRN 155-04-4)	MORFAX (CASRN 95-32-9)	DTDM (CASRN 103-34-4)
<b>Fish 96-h LC<sub>50</sub> (mg/L)</b>	<b>0.73 – 11</b>	<b>1.8 – 13.3</b>	No data 0.73-11 (RA)	No data 87.6 (e)	<b>1.6 – 3.7</b>
<b>Aquatic Invertebrates 48-h EC<sub>50</sub> (mg/L)</b>	<b>2.9 – 4.1</b>	<b>19 (m)</b>	No data 2.9-4.1 (RA)	No data 8.1 (e)	<b>4.5</b>
<b>Aquatic Plants 96-h EC<sub>50</sub> (mg/L)</b>	<b>0.25 (biomass)</b>	<b>0.4 (biomass) 0.3 (growth)</b>	No data 0.25 (RA)	No data 3.0 (e)	<b>29 (biomass)</b>
<b>Chronic Toxicity to Fish 89-d (mg/L)</b>	<b>0.06 (MATC)</b>	No data 0.06 (RA)	No data 0.06 (RA)	–	–
<b>Chronic Toxicity to Invertebrates 21-d (mg/L)</b>	<b>0.39 (m) (MATC)</b>	No data 0.39 (RA)	No data 0.39 (RA)	–	–

**Bold = measured data;** MATC = maximum acceptable toxicant concentration;  
(RA) = Read across; (e) = estimated data;