SIDS Initial Assessment Report

For

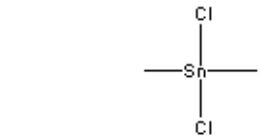
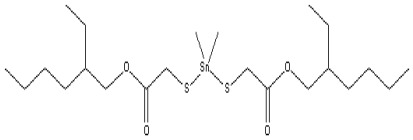
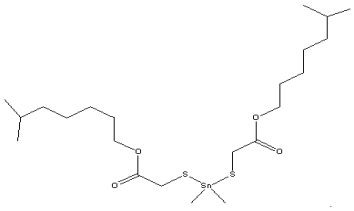
SIAM 23

Jeju, South Korea, 17–20 October 2006

1. Category Name:	Dimethyltin dichloride and selected thioesters
2. Chemical Names and CAS Numbers:	Dimethyltin dichloride (CAS No. 753-73-1) Dimethyltin bis(2-ethylhexylmercaptoacetate) (CAS No. 57583-35-4) Dimethyltin bis(isooctylmercaptoacetate) (CAS No. 26636-01-1)
3. Sponsor Country:	United States of America Oscar Hernandez Director, Risk Assessment Division (7403M) U.S. Environmental Protection Agency 1200 Pennsylvania Ave, N.W. Washington, DC 20460 Phone: 202-564-7641
4. Shared Partnership with:	Lead Organization: Organotin Environmental Programme (ORTEP) Association, Stabilizer Task Force Cooperating companies: Arkema Inc. Chemtura Corporation Reagens Canada, Ltd. Rohm and Haas Co. Songwon Industrial Company, Ltd.
5. Roles/Responsibilities of the Partners:	

• Name of industry sponsor /consortium	Organotin Environmental Programme (ORTEP) Association – Stabilizer Task Force Contact person: Stuart Currie, 425-458-6200
• Process used	See comments
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme?	These substances are sponsored by the Organotin Environmental Programme (ORTEP) Association under the ICCA Initiative.
7. Review Process Prior to the SIAM:	The industry consortium reviewed existing data, collected new data, and prepared the updated IUCLID dossier and draft versions of the SIAR and SIAP.
8. Quality check process:	The studies were scored for data reliability using the EPA-approved Klimisch et al. (1997) scoring system.
9. Date of Submission:	
10. Date of last Update:	
11. Comments:	Ecotoxicity and health effects studies assigned a validity rating of 1 (valid without restriction) or 2 (valid with restriction) (Klimisch et al. 1997) are included in this SIAR, unless otherwise noted

SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	Dimethyltin chloride and selected thioglycolate esters	
Structural Formula Chemical Names and CAS Registry Numbers		Dimethyltin dichloride (DMTC), CASRN 753-73-1
		Dimethyltin bis[2-ethylhexyl thioglycolate] [DMT(EHTG)], CASRN 57583-35-4
		Dimethyltin bis[isooctyl thioglycolate] [DMT(IOTG)], CASRN 26636-01-1

SUMMARY CONCLUSIONS OF THE SIAR

Category Rationale

DMTC, DMT(EHTG), and DMT(IOTG) are considered one category of compounds for mammalian studies via the oral route. The justification for this category is based on structural similarities and the demonstrated rapid conversion of all of the esters to the DMTC when placed in simulated mammalian gastric contents [0.07M HCl] under physiological conditions. The data from the simulated gastric reaction study of DMT(EHTG) shows that essentially all DMT(-EHTG) is converted to DMTC at pH 1.5 within 0.5 hours. Thus, DMTC is the appropriate surrogate for mammalian toxicology studies via the oral route.

Acute toxicity, sensitization, irritation and *in vitro* genotoxicity are not covered under the category approach and the results of the mammalian *in vivo* tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was not used for the ecotoxicity and environmental fate endpoints. The considerable difference in the structures of the labile ligands causes differences in water solubility between the alkyltin chloride and thioesters affecting their respective bioavailabilities and distribution in the environment. Furthermore, DMT(EHTG) and DMT(IOTG) will degrade in aqueous solution such that organisms will be exposed to the parent material and their different

degradation products. DMTC is not an appropriate surrogate for the thioesters for the ecotoxicity and environmental fate endpoints.

Analogue Rationale

Data for DMT(EHTG) and DMT(IOTG) are used interchangeably because they are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. In addition, the breakdown products of DMT(EHTG) and DMT(IOTG) are the thioglycolate esters (EHTG and IOTG), which have the common degradates, thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or isooctanol). EHTG and IOTG also have similar physicochemical and toxicological properties.

EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed in the OECD HPV Chemicals Program.

Human Health

The majority of toxicology studies were conducted with commercial mixtures having high dialkyltin to monoalkyltin ratios.

No toxicokinetic data are available for DMTC, however studies were conducted with DMT(EHTG) in which simulated gastric fluid (0.07M HCl under physiological conditions) converted this substances to dimethyltin chloride and the respective organic acid. *In vitro* data for DMTC and DMT esters indicate the dermal penetration of these compounds is low. Published data indicate that dimethyltin can cross the placenta.

Acute oral LD50s for the dimethyltin compounds have a wide range, but the most reliable data place the LD50 at approximately 400 mg/kg for DMTC and approximately 1200 mg/kg for the thioglycolates. The most reliable inhalation LC50 values range from 115 (4-h aerosol exposure) for DMTC to 132,000 mg/m3 for DMT(IOTG) and comparisons are complicated by inadequate descriptions of the aerosol in some studies. Dermal LD50 values in rabbits ranged from 380 to >2000 mg/kg for DMTC and >1050 to >3100 mg/kg for the thioglycolates. Again, study comparisons are complicated by inadequate descriptions of the tested compounds.

DMTC is corrosive to skin and eyes. DMT(EHTG)/(IOTG) are slightly to moderately irritating to skin and minimally to not irritating to eyes. DMTC is not a sensitizer. Data on DMT(2-EHTG) and DMT(IOTG) suggest that the DMT thioesters are weak sensitizers and the hydrolysis products, EHTG or IOTG, are sensitizers.

There are two repeated-dose oral studies of DMTC (90-day drinking water and 90-day feeding). The results are consistent and they are considered in tandem. DMTC had a NOAEL of 15 ppm in feed (~1.0 mg/kg/d). The critical toxic effect in both studies was neurotoxicity; tremors and convulsions were observed in a dose-related manner. Histopathology (feed study) confirmed neuronal death in the cerebellum and lesions in the hippocampal region, the piriform, entorhinal, and perirhinal cortices, the amygdala, the olfactory nuclei and the tenia tecta. The NOAEL was 15 ppm (feed) and the LOAEL was 25 ppm (water; ~2.2 mg/kg bw day).

DMTC was negative in two Ames tests, with and without metabolic activation, but was positive in Salmonella typhimurium strain TA100 without metabolic activation in another test. DMT(EHTG) was negative in a standard Ames assay. Although DMTC was positive in an in vitro chromosomal aberrations assay with metabolic activation, it was negative in an in vivo mouse micronucleus test. Based on these observations the overall conclusion is that DMTC does not have genotoxic

potential.

Data from DMTC repeated dose studies with rats indicated no gross or histopathological effects on the reproductive organs of either sex. In separate studies, DMTC was administered to rats from days 7 to 17 of gestation at doses of 5, 10, 15, and 20 mg/kg bw/day. The NOAEL for developmental toxicity was 10 mg/kg-bw/day, with reduced fetal weight observed at 15 mg/kg-bw/day, and fetal death, cleft palate and other effects observed at 20 mg/kg bw/day, which also resulted in severe maternal toxicity (20% deaths, vaginal bleeding, tremors and other effects). In the same study, DMTC was also administered at 20 and 40 mg/kg bw/day at 4 different time periods during gestation (all 3-day intervals). Effects included increased numbers of fetuses with skeletal variations, cervical ribs, and/or splitting of first cervical vertebral arch at 40 mg/kg bw/day in the protocols where DMTC was administered on days 7-9 or 13-15 of gestation. At 40 mg/kg bw/day and days 16-17 of gestation, the number of fetuses with kinked ureters were statistically increased. Maternal toxicity in this portion of the study was limited to the gestation day 10-12 protocol at both 20 and 40 mg/kg bw/day. DMTC was fetotoxic at maternally toxic doses.

Environment

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals in their molecular structure; therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported below.

DMTC is a solid at room temperature and melts at 90°C, boils at 188-190°C, has a calculated vapor pressure of 0.25 hPa at 25°C , and is soluble in water (823 g/L). The log Kow is -2.18, and is not likely to bioaccumulate (log BCF=0.5). DMTC is not readily biodegradable, but atmospheric degradation occurs by photochemical induced hydroxyl radicals, with a half-life of 7.9 days. If released to the environment, DMTC is expected to partition primarily into water (51.6%) and soil (47.3%).

In water, DMTC undergoes rapid degradation by hydrolysis and is expected to hydrolyze within minutes. It is expected that the chlorines in DMTC will be displaced to form di-methyltin hydroxide which eventually precipitates as the oxide. (The alkyltin moiety (DMT) was hydrolytically stable at pH 4, 7, and 9 (t1/2 > 1year at 25°C)).

DMTC has sufficient water solubility that it can be studied in water using analytical methods that involve derivitization. This analysis method only measures the amount of the alkytin moiety, and can determine if the alkyltin itself is degrading. This method does not identify the other ligands attached to the tin, and thus hydrolysis of the chloride on tin to the hydroxide is NOT detected using this method. DMT(EHTG) is a liquid at room temperature, has a freezing point of -75 to -65°C, decomposes at ≥ 290°C, and a calculated vapor pressure of 0.004 hPa at 25°C. DMT(EHTG) is slightly soluble in water (0.1–4.9 mg/L), hydrophobic (log Kow = 8.48), and has a moderate potential to bioaccumulate (log BCF = 2.7). DMT(EHTG) is not readily biodegradable, but is atmospherically degraded by hydroxyl radicals and UV radiation. If released to the environment, DMT(EHTG) is predicted to partition to sediment (68%) and soil (28%), with smaller amounts in water (3.8%) and air (0.3%). DMT(IOTG) is predicted to partition into sediment (70.4%) and soil (27.5%), with smaller amounts in water (1.9%) and air (0.13%).

DMT(IOTG) and DMT(EHTG) are sparingly soluble in water as shown by the data for DMT(EHTG) that estimates solubility as 0.1-4.9 mg/L. In water, DMT(EHTG)/IOTG undergo rapid degradation by hydrolysis. Although there is no stability data for DMT(EHTG)/(IOTG),

data for other organotins [DOTC, DBTL, and DBT(EHTG)] indicate that the dimethyltin compounds are expected to hydrolyze within minutes to hours in water. . The thioester ligands on DMT(EHTG)/(IOTG) will be rapidly displaced to form dimethyltin hydroxide which eventually precipitates as the oxide. It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioester ligands, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and either ethylhexanol or isooctanol, respectively.

In the ecotoxicity tests the organisms were most likely exposed to parent substance as well as hydrolysis/degradation products.

DMTC was not acutely toxic to *B. rerio* at 100 mg/L. The 96-h LC50 for *P. promelas* was reported to be 320 mg/L. The 48-h EC50 to *D. magna* was 17 (12–24) mg/L. The 72-h EC50 (growth rate) for *S. subspicatus* was reported as 37 mg/L.

Acute aquatic toxicity data for DMT(EHTG) are available for fish, daphnia, and algae; and chronic aquatic toxicity data are available for daphnia. A 96-h LC50 for *P. promelas* was reported to be >1000 mg/L. The 48-h EC50 for *D. magna* was 32 mg/L. The 72-h EC50 for *P. subcapitata* on growth and cell density values are 270 mg/L and 120 mg/L, respectively. In a 21-day *D. magna* reproduction study, LC50 for parental survival was 1.0 mg/L; however, a clear dose-response relationship was not observed. The overall NOEC and LOEC were 0.46 mg/L (10% WAF) and 2.3 mg/L (50% WAF), respectively.

Exposure

DMTC is primarily used as an intermediate in the synthesis of organotin chemicals and, to a lesser extent, as a coating on glass. In 2000, worldwide production of DMTC was estimated at 1,000 to 5,000 metric tons [MT]. DMT(EHTG) is used in the production of films, sheets, injection moldings, pipes, sidings, and other applications where high thermostability is required. DMT(EHTG) has clearance in many countries for use in potable water pipes, and also is approved for use in food contact applications. In 2000, worldwide production of DMT(EHTG) was estimated at 5,000 to 10,000 MT. Use of DMT(IOTG) has been gradually replaced by DMT(EHTG) over approximately a ten year period.

DMT(EHTG)/(IOTG) is added to polyvinyl chloride (PVC) and chlorinated polyvinyl chloride (CPVC)as a heat stabilizer. After being blended into the PVC and CPVC resin, the stabilizers remain there throughout the subsequent processing steps. Dimethyltins may also be used in other PVC articles, such as window profiles, house siding, fences and decking. The amounts of stabilizer that can be used in the PVC, or the levels of dimethyltins that can be extracted into food and water are controlled. In one study, levels of dimethyltin extracted from PVC packaging materials by food simulants were below the specific migration limit established for methyltin compounds (0.18 mg Sn/kg).

Maximum dimethyltin concentrations of 400 ng Sn/L and 0.27 µg Sn/kg dry weight were reported in water and freshwater and marine sediment, respectively. Dimethyltin stabilizers occur occasionally in raw waste water; however, some research has shown that about 80% of organotins detected in untreated wastewater is associated with suspended solids and are removed from wastewater primarily by sedimentation and adsorption into sewage sludge. Studies have shown that dimethyltins have a half life of about 6 months in the environment.

Dimethyltin was not detected in saltwater in Western Florida or the Gulf of Mexico but was detected in Baltimore Harbor in Maryland with a maximum concentration of 0.1 µg/L. In a Canadian marina (freshwater), a maximum of 0.4 µg/L was found. In U.S. rivers, a mean of 0.004 µg/L was found; in German rivers a maximum of 0.26 µg/L, and in Florida lakes, ponds, and rivers none was detected (<0.008 µg/L).

In Turkey, the maximum sediment concentration of dimethyltin was 0.01 µg/L; in Great Bay, NW,

the maximum sediment concentration was 0.06 µg/L, and in San Diego Bay, the maximum concentration in sediment was 0.003 µg/L. Dimethyltin has been found in fresh water, seawater, and sediment in Canada in about 10 percent of all waters sampled.

In the Mediterranean, dimethyltin has been found in limpet (*Patella caerulea)* at 0.0002 mg Sn/kg in the shell and 0.009 mg Sn/kg in soft parts. In a forested area in Germany, dimethyltin compounds were detected in precipitation.

Dimethyltin compounds have been detected in Canadian drinking water at up to 49.1 ng Sn/L in one survey and up to 6.5 ng Sn/L in another study. In the United States, dimethyltin was found to range from 0.40 to 2.2 ng Sn/L in a limited number of tap water samples from Florida in 1977.

Most PVC and CPVC articles will either be recycled or landfilled at end of life. A portion of the PVC products entering the total solid waste stream will be incinerated, which destroys organotins and converts them to inorganic tin oxides. Concentrations of organotins in leachate samples from sanitary landfills were found to be in the low micrograms per liter range.

RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

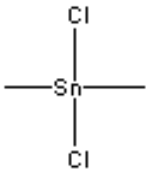
Human Health: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (corrosivity, skin sensitization (EHTG/IOTG), neurotoxicity, and fetotoxicity at maternally toxic doses). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

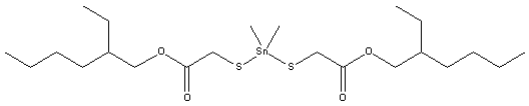
Environment: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.

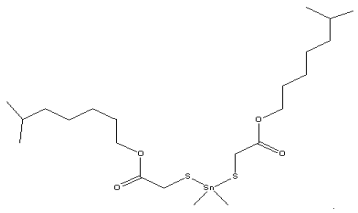
SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substances

CAS Number:	753-73-1
IUPAC Name:	Stannane, dichlorodimethyl-
Molecular Formula:	$C_2H_6Cl_2Sn$
Structural Formula:	
Molecular Weight:	219.67 g/mol
Synonyms:	Dichlorid dimethylcinicity [Czech]; Dichlorodimethylstannane; Dichlorodimethyltin; Dimethyldichlorostannane; Dimethyldichlorotin; Dimethyltin dichloride; Dimethylzinndichloride [German]; DMTC; DMTCl; Tin, dimethyl-, dichloride
Abbreviation Used in this Document	DMTC

CAS Number:	57583-35-4
IUPAC Name:	8-Oxa-3,5-dithia-4-stannatetradecanoic acid, 10-ethyl-4,4-dimethyl-7-oxo-, 2-ethylhexyl ester
Molecular Formula:	$C_{22}H_{44}O_4S_2Sn$
Structural Formula:	
Molecular Weight:	555.4 g/mol
Synonyms:	2-ethylhexyl 10-ethyl-4,4-dimethyl-7-oxo-8-oxa-3,5-dithia-4-stannatetradecanoate; Dimethyltin bis(2-EHMA); Dimethyltin bis(2-ethylhexyl mercaptoacetate); Dimethyltin bis(2-ethylhexylthioglycolate); DMT(EHMA); DMT(EHTG); DMT(2-EHMA)
Abbreviation Used in This Document	DMT(EHTG)

CAS Number:	26636-01-1
IUPAC Name:	Acetic acid, 2,2'-[(dimethylstannylene)bis(thio)]bis-, diisooctyl ester
Molecular Formula:	$C_{22}H_{44}O_4S_2Sn$
Structural Formula:	
Molecular Weight:	555.4 g/mol
Synonyms:	2,2'-[(dimethylstannylene)bis(thio)]bisacetic acid diisooctyl ester; Bis((((isooctyloxy)carbonyl)methyl)thio)dimethyltin; Diisooctyl ((dimethylstannylene)dithio)diacetate; Diisooctyl 2,2'-[(dimethylstannylene)bis(thio)]diacetate; Dimethyl-S,S'-bis(isooctylmercaptoacetate)tin; Dimethyltin bis(IOMA); Dimethyltin bis(isooctyl mercaptoacetate);

	Dimethyltin bis(isooctyl thioglycolate); Dimethyltin-S,S'-bis(isooctyl mercaptoacetate); Dimethyltin-S,S'-bis(isooctyl thioglycolate); Dimethylzinn-S,S'-bis(isooctylthioglycolat) [German]; DMT(IOMA); DMT(IOTG); Stannane, bis(isooctyloxycarbonylmethylthio) dimethyl- Diisooctyl 2,2'-[(dimethylstannylene)bis(thio)]diacetate
Abbreviation Used in This Document	DMT(IOTG)

1.2 Purity/Impurities/Additives

Dimethyltin dichloride

Dimethyltin dichloride (DMTC) is always manufactured as a mixture with monomethyltin trichloride (MMTC, CAS No. 993-16-8), and may be produced as either an aqueous solution or as a solid material. The DMTC content in di/monomethyltin mixtures may range from 10–99% (by weight). Mono/di mixtures having 50% or greater amounts of DMTC are considered as dimethyltin materials and are covered in this SIAR; mixtures having less than 50% DMTC are considered as monomethyltin materials and are covered under the accompanying monomethyltin SIAR. DMTC, MMTC, water (for aqueous solutions), and the technical impurities of trimethyltin chloride and tin tetrachloride account for up to 99% (by weight) of the manufactured product. The amounts of trimethyltin chloride and tin tetrachloride in a di/monomethyltin mixture will vary depending on the di/monomethyltin ratio; therefore, a range of these impurity levels cannot be defined. DMTC contains no chemical additives.

Dimethyltin bis(2-ethylhexyl mercaptoacetate)

Dimethyltin bis(2-ethylhexylmercaptoacetate) [DMT(EHTG)], always manufactured as a mixture with monomethyltin tris(2-ethylhexylmercaptoacetate) [MMT(EHTG), CAS #57583-34-3)], is produced through reaction of a mixture of DMTC and MMTC with 2-ethylhexylmercaptoacetate (EHTG, CAS No. 7659-86-1). The di/monomethyltin ratio matches that of the starting chlorides, with the dimethyltin content typically ranging between 10-99% (by weight). Mixtures having 50% or greater amounts of DMT(EHTG) are considered as dimethyltin materials and are covered in this SIAR; mixtures having less than 50% DMT(EHTG) are considered as monomethyltin materials and are covered under the accompanying monomethyltin SIAR. These di:mono-methyltin mixtures can contain impurities at trace levels, such as trimethyltin compounds (levels typically < 0.1% calculated as tin), residual ethylhexyl mercaptoacetate, MMTC, and DMTC. Because the production of di/monomethyltin chlorides is very well controlled, the amount of trimethyltin in the final product can be tightly controlled. DMT(EHTG) generally contains no chemical additives.

Dimethyltin bis(isooctyl mercaptoacetate)

Dimethyltin bis(isooctylmercaptoacetate) [DMT(IOTG)], commonly manufactured and used in combination with monomethyltin tris(IOMA) (CAS No. 54849-38-6), is produced through reaction of a mixture of mono- and dimethyltin chlorides with isooctylmercaptoacetate (CAS No. 25103-09-

7), similar to DMT(EHTG). Historically, IOTG was used; however, today the predominant product line is the EHTG.

1.3 Physico-Chemical Properties

DMT(EHTG) and DMT(IOTG) are isomers, and data for these materials are used interchangeably. Also, current versions of EPIWIN, developed by Syracuse Research Corporation, have not been validated for estimating endpoints for chemicals that contain metals in their molecular structure; therefore, estimated values derived from the EPIWIN models should be used with caution. The physico-chemical data for DMTC and DMT(EHTG)/(IOTG) are summarized in Tables 1 and 2 below.

Table 1 Summary of physico-chemical properties of DMTC

Property	Protocol	Value	Reference
Physical state (ambient)	Not Applicable	Colorless liquid or gray solid	
Melting point	Unknown	90°C	CRC Handbook 1979
Boiling point	Unknown	188–190°C at 1013.3 hPa	CRC Handbook 1979
Relative density	Unknown	1.4 g/cm^3	Springborn Laboratories 1993
Vapour pressure	Calculation (MPBPWIN v1.41)	0.25 hPa at 25°C [1]	USEPA 2000a
Water solubility	OECD 105	823 (819.8–826.2) g/L at 20°C	Spruit and Schilt 2003
Partition coefficient n-octanol/water (log value)	OECD 107	-2.18 at 22°C	Spruit and Schilt 2003
Henry's law constant	Calculation (HENRYWIN v3.10)	6.88 × 10E-8 atm-m^3/mol	USEPA 2000b

1 Measured vapor pressure values for the organotins are difficult to obtain. The named substance contains a certain percentage of impurities and the lower molecular weight impurities will volatilize more readily and, therefore, influence the measured vapor pressure. In order to confirm that the vapor pressure is completely attributable to the named substance, a derivatization method to analyze the organotins would have to be used. This method involves ligand exchange and currently there is no analytical method available that allows us to quantify the entire organotin compound with its associated ligands. Therefore, only calculated vapor pressure values are provided.

Table 2 Summary of Physico-Chemical Properties of DMT(EHTG)/(IOTG)

Property	Protocol	Value	Reference
Physical state (ambient)	Not Applicable	Colorless liquid	
Melting point	Measured (DSC)[1]	-75 to -65°C	Crompton GmbH 2001
Boiling point	Measured (DSC)[1]	≥ 290°C (decomposition)	Crompton GmbH 2001
Relative density	Unknown	1.18 g/cm^3	BASF 2000
Vapour pressure	Calculation (MPBPWIN v1.41)	0.0044 hPa at 25°C[2]	USEPA 2000a
Water solubility	Estimated (100% Water Accommodated Fraction or Water Soluble Fraction)	0.1 to 4.9 mg/L (slightly soluble)[3]	de Roode and de Haan 2004
Partition coefficient n-octanol/water (log value)	Calculation (KOWWIN v1.67)	8.48	USEPA 2000c
Henry's law constant	Calculation (HENRYWIN v3.10)	6.755 atm-m^3/mol	USEPA 2000e

1 DSC = Differential Scanning Calorimetry

2 Measured vapor pressure values for the organotins are difficult to obtain. Similar problems exist for measuring vapor pressure as for water solubility and partition coefficient. The named substance contains a certain percentage of impurities and the lower molecular weight impurities will volatilize more readily and, therefore, influence the measured vapor pressure. In order to confirm that the vapor pressure is completely attributable to the named substance, a derivatization method to analyze the organotins would have to be used. This method involves ligand exchange and currently there is no analytical method available that allows us to quantify the entire organotin compound with its associated ligands. Therefore, only calculated vapor pressure values are provided.

3 DMT(EHTG)/(IOTG) are only slightly soluble in water. For estimates such as the ones given here a precaution is appropriate. Low levels of impurities may be present, even in a high purity organotin substance. These impurities often are more soluble in water than the named substance and confound the measurement of water solubility of the named substance to a significant degree. Thus, the reported solubility values may not be due entirely to the named substance and any subsequent use of the water solubility values to predict environmental behaviour of the named substance must carefully consider the limitations inherent in the measurement of this parameter.

1.4 Category Justification

DMTC, DMT(EHTG), and DMT(IOTG) are considered one category of compounds for mammalian studies via the oral route. The justification for this category is based on structural similarities and the demonstrated rapid conversion of the esters to DMTC when placed in simulated mammalian gastric contents [0.07M HCl] under physiological conditions (pH 1-2). Data from the simulated gastric reaction study of DMT(EHTG) showed that essentially all DMT(EHTG) is converted to DMTC at pH 1.5 within 0.5 hours. Thus, DMTC is the appropriate surrogate for mammalian toxicology studies of DMT(EHTG)/(IOTG) via the oral route. Because DMT(EHTG) and DMT(IOTG) are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand, they can be considered toxicologically equivalent, and a similar rate of hydrolysis is expected for both dimethyltin thioesters.

Acute toxicity is not covered under the category approach, and acute oral toxicity was evaluated individually for each material. The gastric reaction is dependent upon dissolution of the test substance. With respect to inhalation and dermal mammalian toxicity, the esters have much higher molecular weights and considerably lower volatility than the chloride. The high molecular weights of the esters reduces their potential for absorption via the dermal route, and their volatility reduces their potential for absorption via the inhalation route relative to the chloride.

Sensitization, irritation and *in vitro* genotoxicity also are not covered under the category approach and the results of the mammalian *in vivo* tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes because there is no contact with gastric contents. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was not used for the ecotoxicity and environmental fate endpoints. The considerable difference in the structures of the labile ligands causes differences in water solubility between the alkyltin chloride and thioesters affecting their respective bioavailability and distribution in the environment. Furthermore, DMT(EHTG) and DMT(IOTG) will degrade in aqueous solution such that organisms will be exposed to the parent material and their different degradation products. DMTC is not an appropriate surrogate for the thioesters for the ecotoxicity and environmental fate endpoints.

1.5 Analogue Justification

Data for DMT(EHTG) and DMT(IOTG) are used interchangeably because they are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. Historically, the IOTG stabilizers were the predominant commercial products; however, current products are manufactured using EHTG. Where available, data for the IOTG compound are reported; however, no new testing of this compound was conducted. Where data gaps exist for the IOTG compound, new or existing data for the corresponding EHTG compound are reported for both compounds. Validation of this analogue and category approach comes from examination of appropriate comparative toxicology data of DMT(EHTG) and DMT(IOTG) (Table 3).

Table 3 Comparative Toxicology Data for the DMT(EHTG) and DMT(IOTG)

Endpoint	DMT(EHTG)	DMT(IOTG)
Acute oral toxicity	Rat LD50: 1150 mg/kg bw (M/F) 1710 mg/kg bw (M)	Rat LD50: 1090–1735 mg/kg bw (M/F) 1214 mg/kg bw (M/F)
Acute inhalation toxicity	Rat LC50: 240 mg/L	Rat LC50: 132 mg/L
Acute dermal toxicity	Rabbit LD50: > 1050 mg/kg bw	Rabbit LD50: > 3100 mg/kg bw

M = Male, F = Female

The acute toxicity of DMT(EHTG) and DMT(IOTG) via oral, inhalation, and dermal routes has been assessed and the data support essentially the identical conclusion for both compounds, i.e., DMT(EHTG) and DMT(IOTG) are of low to moderate toxicity.

In addition, the breakdown products of DMT(EHTG) and DMT(IOTG) are the thioglycolate esters (EHTG and IOTG). The thioglycolate congeners (EHTG and IOTG) are two octyl (C-8) esters of thioglycolic acid whose ester linkage to the tin is identical. Both EHTG and IOTG are hydrolytically unstable, and have common degradates which are thioglycolic acid (TGA; CAS No. 68-11-1) and either 2-ethylhexanol (CAS No. 104-76-7), an 8-carbon alcohol, or 5-methyl heptanol, also called iso-octanol. Melting point, boiling point, vapour pressure, and water solubility values for the thioglycolates are consistent (Table 4), as expected for close structural analogues. Partition coefficients further suggest that their kinetic behaviour in mammalian and aquatic biological systems would not be markedly different. These similarities suggest that the two thioglycolate esters

would be toxicologically similar. Thus, in vivo mammalian toxicity, genetic toxicity, reproductive and developmental toxicity data for DMT(EHTG) are representative of DMT(IOTG).

EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed in the OECD HPV Chemicals Program. Additional data can be found in the EHTG and IOTG documents from SIAM 23.

Table 4 Summary of Physico-Chemical Properties of EHTG and IOTG

Property	EHTG	IOTG
Physical state	Liquid	Liquid
Melting point	< -50°C	< -50°C
Boiling point	119.5-171.1°C @ 9.5 hPa	117.5-161.8°C @ 9.5 hPa
Relative density	0.97-0.98 g/cm^3 @ 20°C	0.98 g/cm^3 @ 25°C
Vapour pressure	0.97 hPa @ 25°C	0.19 hPa @ 25°C
Water solubility	4.7 mg/L @ 20°C	10.6 mg/L @ 20°C
Partition coefficient n-octanol/water (log value)	2.4	3.96

Source: SIDS Initial Assessment Report for SIAM 23, Esters of Thioglycolic Acid. Prepared by the Thioesters Association. May 2006.

2 GENERAL INFORMATION ON EXPOSURE

In the U.S., organotins were placed on the drinking water contaminant candidate list in 1998 partly because mono- and di-organotins used in chlorinated PVC pipes were of sufficient concern to warrant further investigation (63 FR 10273). Organotins remain on the contaminant candidate list (published in February 2005) because they are known or anticipated to occur in public drinking water systems (70 FR 9071).

Dimethyltin compounds are produced outside the European Union (EU) by the cooperating companies in this HPV consortium and are imported for use in the EU. Some companies may import the methyltin intermediates from North America into Europe and produce the final stabilizer in Europe; others may import the finished stabilizer from North America into Europe.

In Australia, organotin compounds are used extensively in PVC applications that include vegetable oil, fruit juice, and wine bottles as well as shampoos and cosmetic containers. Several companies supply organotin stabilizers in Australia (Scheirs 2003).

2.1 Production Volumes and Use Pattern

DMTC

In 2000, worldwide production of DMTC was estimated at 1,000 to 5,000 metric tonnes (ORTEP Association 2004). DMTC is always manufactured as a mixture with mono-methyltin trichloride (MMTC). While the mono/dimethyltin chloride mixtures, or “crudes”, are primarily used as intermediates for the production of stabilizers and other organotin chemicals, the higher purity DMTC produced is generally used in glass coating applications.

DMT(EHTG)

In 2000, worldwide production of DMT(EHTG) was estimated at 5,000 to 10,000 metric tonnes (ORTEP Association 2004). DMT(EHTG), always manufactured as a mixture with MMT(EHTG), is a highly efficient heat stabilizer in polyvinyl chloride (PVC). Dimethyltin mercaptoacetate-based stabilizers are widely used in the production of films, sheets, injection moldings, pipes, sidings, and other PVC applications where high thermo-stability is required. These materials also have clearance in many countries for use in food contact and potable water pipe applications.

DMT(IOTG)

Historically the IOTG compound was used in production; however, today the predominant product line is the 2-ethylhexylmercaptoacetate (EHTG). The migration of IOTG to EHTG was primarily an economic decision and gradual decrease in the use of IOTG occurred over a period of 10 years. Production volumes are not available for IOTG.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

DMTC is used as an industrial intermediate in the production of organotin compounds by the manufacturer or is sold to other chemical companies for conversion to other products. DMTC also is marketed for use in glass coating applications. Releases to the environment would occur as part of the production of this intermediate or its conversion to other dimethyltin products. Releases from production facilities are regulated in many countries, although no measurements have been made of dimethyltins.

The process of using DMTC in glass coating applications is well established and the process does not leave any organotin residue on the glass surface, as it is converted to tin oxide through heating to over 400^{o}C. Generally, treatment processes for the air (after coating has taken place) are intended to remove dust from the air and may include using a scrubber, using a furnace to convert any remaining DMTC to tin oxide, or venting the spent air to the atmosphere.

DMT(EHTG), always manufactured as a mixture with MMT(EHTG), is added to polyvinyl chloride (PVC) and chlorinated polyvinyl chloride (CPVC) as heat stabilizers intended to preserve the polymeric structure and properties of the resins during the final stages of fabrication into finished articles. After being blended into the PVC and CPVC resin, the stabilizers remain there throughout the subsequent processing steps.

All systems are designed and maintained to ensure that moisture is kept away from the resin compound, since the presence of water creates significant problems during processing. Therefore, losses to water during blending and melt processing are very low, as these are designed to be “dry” processes. Furthermore, water is not used on a regular basis to clean equipment, wash out vessels, etc., and no wastewater is generated. Compounded PVC and CPVC material is solid and any spillage is cleaned up by sweeping or vacuum. Once the PVC or CPVC is melt processed into a final part, most of the dimethyltin chemicals are strongly held within the resin although some leaching of dimethyltin compounds may occur from some PVC/CPVC products (see Section 2.3.2).

During melt processing of PVC and CPVC, there is the possibility that dimethyltins (or other ligands unspecified) can be released into the atmosphere. Measurements by Nowak (2003) of DMT released during a PVC calendering operation show the values to be 0.211% of the dimethyltin processed being released (RPA 2003, pg. 29).

Dimethyltin Exposure. Dimethyltin chemicals either leach out of PVC and CPVC articles, or are released into the atmosphere during the processing described above. As discussed by Muller (1989), there are a range of organotin chemicals that are in the PVC after processing which might leach out. However, these chemicals that leach out of PVC articles into the environment will be hydrolyzed to the corresponding dimethyltin cations and associated anions (RPA 2003). These types of releases are discussed below, and the reader is also referred to the report by RPA (2003), where an in-depth discussion of these releases is provided.

Leaching. When tested, water pipes showed an initial release of dimethyltins, which was followed by decreased releases until low levels of release were reached (Wu et al. 1989, Al-Malack 2001, Hoch 2001, Boettner et al. 1981). These results are explained as a leaching of dimethyltin from the surface, and that the bulk of the organotin is tightly held within the resin matrix. Leaching, however, can lead to some concentrations in drinking water distribution systems and may lead to exposure from PVC/CPVC products. Sampling of distribution systems is discussed in Section 2.3.2.

Regulatory bodies that have approved of the use of methyltins in potable water systems set limits on the amount of tin that can migrate, and in the U.S., the time over which such migration must fall to a small number, for example ANSI/NSF Standard 60. Other articles, such window profiles and building siding that have methyltin stabilizers will show the same type of leaching behavior, i.e., initial level falling to a low level. Chlorinated PVC may result in leaching over a longer time period after installation than PVC (63 FR 10283).

Exposure from food packaging also is regulated, with limits on either the amount of migrated dimethyltin, or the amount of dimethyltin the food packaging material can contain (CEC 2003, 21 CFR 178.2650). The U.S. Food and Drug Administration limits the use of di/monomethyltins to no more than 2% by weight. The EU Scientific Committee for Food (CEC 2003) established specific migration limits (SMLs) for tin stabilisers in food contact applications; limits for dimethyltin compounds are 0.18 mg Sn/kg (CEC 2003).

Environmental Fate. Several studies have been done to examine environmental levels of dimethyltins and their fate. Regarding environmental fate, most PVC articles will either be recycled or landfilled at end of life. Although PVC products are not generally incinerated, any organotin products that are incinerated will be destroyed and converted to inorganic tin oxides (ATSDR 2005).

Some research shows that approximately 80% of organotins detected in untreated wastewater are associated with suspended solids and were removed from wastewater primarily by sedimentation and adsorption into sewage sludge (Fent 1996).

The long-term behaviour of DMTC in the terrestrial environment was evaluated under simulated landfill conditions in a controlled experiment using sandy and organic soils. Soils were spiked via sewage sludge with DMTC at concentrations of 10, 100 and 500 ng Sn/g soil. Aged PVC samples were inspected, and leachate and gas were monitored for product-specific emissions. Mitcherlich vessels (3 month duration) or a lysimeter (6 month duration). Estimated half-lives were 2-6 months for DMT (Terytze et al. 2000). This is similar to the value put forth by Maguire (1991) in a study on organotins for Environment Canada (1993).

Of equal importance when assessing environmental levels of dimethyltins is the fact that methyltins are formed in the environment by microbial systems through the methylation of inorganic tin (Maguire 1991; Hoch 2001; Thayer 1992, 1993; Erŕecalde et al. 1991; Fatoki 1997). Pure strains of two microorganisms, *Pseudomonas fluorescens* and *Schizosaccharomyces pombe,*

biotransformed monobutyltin trichloride (MBTC) directly into dimethyltin. *Ps. fluorescens* metabolized 10% of the MBT producing 10% dimethyltin; *Schiz. pombe* metabolized 13% of the MBT producing 10% dimethyltin and 3% trimethyltin (Erfecalde et al. 1991). Hamasaki et al. (1991) reported on the abiological methylation of inorganic tin. Methyl donors (i.e., ethanol, acetic acid and propionic acid) produced small amounts (0.001-0.3%) of methyltins from inorganic tin under controlled experimental conditions. Hamasaki et al. (1991) also found that methyltin production increased at pH 4-8, and decreased with increasing concentrations of sodium chloride, indicating that the methylation of inorganic tin occurs more easily in freshwater than in seawater. Hamasaki et al. (1995) reported that inorganic tin (II) and (IV) can be methylated under normal environmental conditions, and that factors affecting chemical methylation, including pH, temperature, dissolved oxygen, light irradiation, and the availability and concentration of other counter ions in water vary reaction conditions. Landfill leachate may directly enter the environment. Mersiowsky et al. (2001) and Mersiowsky and Ejlertsson (1999) found that the concentration of organotins in leachate samples from sanitary landfills were found to be in the low micrograms per liter range. In addition, it is expected that most leachate would be treated at on-site water treatment facilities or released into a municipal sewer. If landfill leachate should directly enter the environment, there would be considerable dilution of the leachate resulting in lowered environmental concentrations.

Environmental Levels. In a review of several studies, maximum dimethyltin concentrations of 400 ng Sn/L and 0.27 µg Sn/kg dry weight were reported in water and freshwater and marine sediment, respectively (Summer et al. 1996). Donard et al. (1993) reported dimethyltin concentrations of 132 ng Sn/L in influent, 40 ng Sn/L in activated sludge, and 22 ng Sn/L in effluent.

Dimethyltin was not detected in saltwater in Western Florida (< 0.005 µg Sn/L) or the Gulf of Mexico (< 0.007 µg Sn/L) but was detected in Baltimore Harbor in Maryland with a maximum concentration of 0.1 µg Sn/L (Hall and Pinkney 1985 as cited in Eisler 1989). In a Canadian marina (freshwater), a maximum of 0.4 µg Sn/L was found (Maguire et al. 1982 as cited in Eisler 1989). In U.S. rivers, a mean of 0.004 µg Sn/L was found; in German rivers a maximum of 0.26 µg Sn/L, and in Florida lakes, ponds, and rivers none was detected (< 0.008 µg Sn/L) (Hall and Pinkney 1985 as cited in Eisler 1989).

In Turkey, the maximum sediment concentration of dimethyltin found was 0.01 µg Sn/L (Tugrul et al. 1983 as cited in Eisler 1989); in Great Bay, New Hampshire, the maximum sediment concentration was 0.05 µg Sn/L (Randall et al. 1986 as cited in Eisler 1989), and in San Diego Bay, the maximum concentration in sediment was 0.003 µg Sn/L (Hall and Pinkney 1985 as cited in Eisler 1989).

Other information from Canada shows that dimethyltin has been found in fresh water, seawater, and sediment in Canada at concentrations similar to other countries, and was found in about 10 percent of all waters sampled (http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/ps11-1sp1/non_pest_org_comp/...).

In a monitoring program in the northeastern Mediterranean in 1980, limpit (Patella caerulea) contained a mean dimethyltin concentration of 0.0002 mg Sn/kg fresh weight in the shell and 0.009 mg Sn/kg fresh weight in soft parts (Tugrul et al. 1983 as cited in Eisler 1989).

In Northeast Bavaria, Germany in a forested area, dimethyltin compounds were detected in bulk precipitation, throughfall, and fog during 2001-2002 (Huang et al. 2004 as cited in ATSDR 2005). Median total organotin concentrations were 5.83, 14.6, and 57.1 ng Sn/L, respectively, in the above types of precipitation.

Organotins were found at eight sites that are on the National Priority List of hazardous waste sites in the United States. (It is not clear how many sites were measured for organotin.) No organotin concentrations were found in air or groundwater at these sites; but concentrations were found in surface water at 1 of 8 sites in sediment at 4 of the 8 sites, and in soil at one site (ATSDR 2005).

A risk assessment by Risk and Policy Analysts Limited, Inc. (RPA 2002, updated 2003) conducted for the European Commission assessed the risks to human health and the environment associated with the use of organotin compounds in Europe. Data used in the risk assessment were provided by various industry groups and supplemented using the EUSES model. RPA (2002, updated 2003) concluded that environmental risks for the aquatic compartment from dimethyltin stabilizers were unlikely to be a concern at the regional and local level. However, methyltins are imported into Europe; therefore, risks in regions that produce dimethyltins may differ.

No information is available on release of organotin compounds from the Toxics Release Inventory in the United States because manufacturers are not required to report releases under Section 313 of the Emergency Planning and Community Right-to-Know Act (ATSDR 2005).

Disposal

Tin is not listed as a hazardous waste constituent by the U.S. EPA. Therefore, its disposal is not restricted by federal land disposal restrictions (ATSDR 2005). Most PVC and CPVC articles will either be recycled or landfilled at end of life. Incineration in an approved hazardous waste incinerator converts the organotin to inorganic tin (ATSDR 2005).

2.2.2 Photodegradation

Vapor-phase dimethyltin compounds and the thioglycolate esters (EHTG and IOTG) are expected to be degraded in the atmosphere by reaction with photochemically-produced hydroxyl (OH) radicals. The estimated second-order rate constants and half-lives for these reactions are summarized in Table 5.

Table 5 Estimated Second-order Rate Constants and Half-lives

Compound	Second Order Rate Constant (cm^3/(molecule*sec)	Estimated Half-life	Reference[2]
DMTC	2.72 × 10E-12	7.9 days	USEPA 2000f, (AOPWIN v.1.91)
DMT(EHTG)	29.1 × 10E-12	8.8 hours	USEPA 2000f, (AOPWIN v.1.91)
DMT(IOTG)	27.7 × 10E-12	9.3 hours	USEPA 2000f, (AOPWIN v.1.91)
EHTG	45.7 × 10E-12	2.8 hours	USEPA 2000f, (AOPWIN v.1.91)
IOTG	45.0 × 10E-12	2.8 hours	USEPA 2000f, (AOPWIN v.1.91)

1The mean of the potential cis- and trans-isomers

2 Current versions of EPIWIN, developed by Syracuse Research Corporation, have not been validated for estimating endpoints for chemicals that contain metals in their molecular structure; therefore, estimated values derived from the EPIWIN models should be used with caution.

Ultraviolet (UV) degradation of DMTC in water was determined in a study by Blunden (1983). Approximately 110 and 300 hours of irradiation reduced the DMTC concentration by 20 and 50%, respectively. DMTC in water, irradiated with UV light, degrades to form inorganic tin compounds.

2.2.3 Stability in Water

DMTC

The abiotic degradation of DMTC (99.7%) was evaluated using OECD TG 111. In water, the chloride ligand readily hydrolyzes leaving the alkyltin. The alkyltin moiety (DMT) was hydrolytically stable at pH 4.0, 7.0 and 9.0 (t½ >1 year at 25°C) (de Wolf and Schilt 2005). In water, the chloride ligand on DMTC readily hydrolyzes to tin hydroxide and generates HCl. As the concentration of HCl increases, the chloride reacts back to form DMTC until equilibrium is reached. Thus, this reaction gives an appearance that DMTC is hydrolytically stable.

DMT(EHTG)/(IOTG)

DMT(EHTG)/IOTG) stabilizers have a low water solubility but contain reactive organic ligands (EHTG, IOTG) that undergo rapid degradation by hydrolysis to produce more soluble tin compounds, either by ligand exchange or by hydrolysis of the ligand itself (Bertelo 2001; Schilt et al. 2005):

$$R_xSnL_y + H_2O \rightarrow R_xSnO_{y/2} \ or \ R_xSnOH_y \ or \ R_xSnL_yOH_y$$

Although there are no stability data for DMT(EHTG)/(IOTG), data for other organotins (DBT(EHTG), DBTL, DOTC) indicate that the dimethyltin compounds are expected to hydrolyze within minutes to hours in water, and the alkyltin moiety is hydrolytically stable. The thioglycolate esters on DMT(EHTG/(IOTG) will be rapidly displaced to form dimethyltin hydroxide which eventually precipitates as the oxide (Yoder 2003; Bertelo 2001; Schilt et al. 2005; de Wolf). It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioglycolate esters, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and either ethylhexanol or isooctanol, respectively.

EHTG and IOTG were hydrolytically unstable in tests conducted in accordance with OECD TG 111 (Epona Associates, LLC 2006a,b).

2.2.4 Transport between Environmental Compartments

The results of distribution modeling of DMTC, DMT(EHTG) and DMT(IOTG) using a Level III fugacity model are summarized in Table 6.

Table 6 Results of Distribution Modeling and Partition Percentages for the Dimethyltin Compounds and the Thioglycolate Esters

Compound	Partition Percentage				Reference
	Air	Water	Soil	Sediment	
DMTC	< 1	51.6	47.3	< 0.1	USEPA 2000g (EPIWIN v.3.11)
DMT(EHTG)	0.3	3.8	27.8	68.2	USEPA 2000g (EPIWIN v.3.11)
DMT(IOTG)	0.13	1.9	27.5	70.4	USEPA 2000g (EPIWIN v.3.11)
EHTG	3.8	45.6	49	1.6	USEPA 2000g (EPIWIN v.3.11) as cited in Epona Associates, LLC 2006a
IOTG	1.8	29	68.2	< 1	USEPA 2000g (EPIWIN v.3.11) as cited in Epona Associates, LLC 2006b

Results from the model were obtained using the preferred properties from the dossiers, half-lives calculated by EPIWIN, using equal releases of 1000 kg/hr to air, water, and soil, respectively; and 0 kg/hr to sediment.

Current versions of EPIWIN, developed by Syracuse Research Corporation, have not been validated for estimating endpoints for chemicals that contain metals in their molecular structure; therefore, estimated values derived from the EPIWIN models should be used with caution.

Although the calculated partition percentages using the model may not be precise, they do provide a reasonable estimation as to which compartments the commercial products will migrate until they are able to hydrolyze.

Conclusion

DMTC is predicted to partition primarily to water (52%) and soil (47%); whereas DMT(EHTG) and DMT(IOTG) are predicted to partition primarily to sediment (68-70%) and soil (27-28%). EHTG and IOTG are predicted to partition primarily to water (29-46%) and soil (49-68%).

2.2.5 Biodegradation

Biodegradation studies of DMTC and DMT(EHTG) are summarized in Table 7.

Table 7 Results of Biodegradation Studies of the Dimethyltin Compounds and the Thioglycolate Esters

Compound	Test method	Percent degradation	Result	Reference
DMTC	OECD TG 301F	3% degradation after 28 days	Not readily biodegradable	Hanstveit 2003
DMT(EHTG)/ (IOTG)	Directive 92/69/EEC[1]	38–57 % degradation after 28 days	Not readily biodegradable	BASF 2000
IOTG/EHTG	OECD TG 301B	15% degradation after 29 days	Not readily biodegradable	Epona Associates, LLC 2006b

1 Comparable to OECD TG 301F

Most of this degradation, as measured by CO2 release, is from the breakdown of the EHTG ligands on the dimethyltin. However, it should also be noted that dimethyltins can be broken down through a de-methylation process by microorganisms (Maguire 1991), a process that would not lead to CO2 formation.

No biodegradation studies of DMT(IOTG) or the thioglycolate ester EHTG were found; however, DMT(EHTG) and DMT(IOTG) and IOTG and EHTG are isomers and data for these materials are used interchangeably.

Conclusion

DMTC, DMT(EHTG)/(IOTG) and IOTG/EHTG are not readily biodegradable.

2.2.6 Bioaccumulation

The bioaccumulation of DMTC was experimentally determined in *Artemia franciscana* at nominal concentrations of 10 and 100 mg Sn/L. The BCF was calculated to be 50 (log BCF = 1.7) in water containing 10 mg Sn/L, but fell below 10 at a nominal concentration of 100 mg Sn/L (Hadjispyrou et al. 2001). No experimental data on the bioaccumulation of DMT(EHTG)/(IOTG) were identified. Calculated log BCFs of 0.5 for DMTC and 2.7 for DMT(EHTG)/(IOTG) were determined using BIOWIN (USEPA 2000g). Log BCFs of 0.8 and 0.8 were calculated for the thioglycolate esters, EHTG and IOTG (Epona Associates, LLC 2006a,b). Based on these data, only a low bioaccumulation potential is expected.

Current versions of EPIWIN, developed by Syracuse Research Corporation, have not been validated for estimating endpoints for chemicals that contain metals in their molecular structure; therefore, estimated values derived from the EPIWIN models should be used with caution.

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational Exposure Limit

Occupational exposure limits have been established by a number of authoritative bodies for all organotin compounds as a class. The U.S. Occupational Safety and Health Administration (OSHA) established a Permissible Exposure Limit (PEL) of 0.1 mg/m^3 in air (measured as tin). Furthermore, the American Conference of Governmental Industrial Hygienists (ACGIH) recommends two limits, an 8-hr time-weighted-average [TWA] limit of 0.1 mg/m^3 in air (measured as tin) and a 15-minute-average Short Term Exposure Limit [STEL] of 0.2 mg/m^3 in air (measured as tin). Similar values have been accepted by Australia, Belgium, United Kingdom, Germany, Finland, France, Korea, Austria, Ireland, Sweden, Spain, Singapore, Philippines, New Zealand, Malaysia, Switzerland, Taiwan, Norway, Italy, Hong Kong, The Netherlands, and Denmark.

Dimethyltin stabilizer production. The most prominent routes of potential exposure to dimethyltins in an occupational setting are inhalation and dermal contact. In the production of dimethyltins, the operations are usually sealed to prevent releases to the atmosphere. Exposure in the workplace is controlled through equipment design and administrative controls such as the use of personal protective equipment, as well as regular air monitoring.

PVC Processing. The stabilizers are added, along with other components, to PVC resin to create a PVC compound. Compounding is done in sealed blenders, usually using sealed lines for transfer, at

temperatures up to 120°C. Worker exposure is confined to manual operations, such as material addition, transfer, or sampling.

The standard equipment for processing of the PVC compound into articles, like window profile, film, or pipe, is an extruder or a calender. With processing temperatures between 180 and 200°C, the PVC can degrade. The stabilizers react with the hydrochloric acid released and replacement of the thioester by the dimethyltins chloride gives mixed dimethyltin thioester chlorides, usually for only a small portion of the stabilizer used in the PVC (Muller 1989). At these temperatures, dimethyltin thioesters, or mixture of dimethyltin chloro-thioesters, can be released into the atmosphere around the extruder or calender.

To understand the levels of exposure in PVC processing plants, processors have measured exposure levels over a wide range of operations (Boraiko and Batt 2005). All of these operations involved standard equipment and designs for air handling and venting around the equipment. The data document two types of exposures. For general work in and around the extruders, measured worker exposure levels were between < 0.0001 mg Sn/m^3 to 0.034 mg Sn/m^3; these values are well below the organic tin threshold limit value (TLV) of 0.1 mg Sn/m^3. For those operations that specifically involved manual handling of the organotin stabilizer, the exposure potential was 50% to just above the TLV at 0.102 mg/m^3 (Boraiko and Batt 2005).

2.3.2 Consumer Exposure

Consumers may be exposed to dimethyltins from PVC used in potable water pipes and fittings and from PVC used in food packaging applications. Dimethyltin stabilizers are approved for use in these applications in many regions around the world.

Food Packaging. Extraction work done by Pira International (2001) showed that levels of dimethyltin extracted from PVC packaging materials by food simulants were below the SML established for methyltin compounds (0.18 mg Sn/kg). In the US methyltin stabilizers are approved for us in PVC packaging under regulations that control that amount of stabilizer that can be used added to the PVC (CEC 2003, USA 21 CFR 178.2650, BGA Food Packaging).

Potable Water Pipes. Dimethyltins are used in the production of PVC and CPVC water pipes. These pipes are tested to insure that the amount of dimethyltin leaching into the water meets regulatory requirements (for example ANSI/NSF 60, Regulation JHPA Potable Water pipe, and KIWA Potable Water Pipe). Wu et al. (1989) showed that that after the residual organotin was rinsed away, diffusion of organotins into the water was reported as negligible after about 12 hours (Wu et al. 1989).

Dimethyltin compounds have been detected in Canadian drinking water. Canadian drinking water samples collected in the winter to spring of 1996 from 25 sites and in the autumn of 1996 from 28 sites contained dimethyltin in ranges of < 0.5 to 49.1 ng Sn/L. Dimethyltin was detected at a frequency of 80% in the winter/spring survey and 57 percent in the autumn survey. In a 1996 summer survey, the areas with highest concentrations from the winter-spring survey showed a decrease in 89 percent of the samples (Sadiki and Williams 1999). Tap water in 10 of 22 homes collected in February 1995 from five Canadian municipalities contained dimethyltin compounds at concentrations of < 0.5-6.5 ng Sn/L. No organotin compounds were detected in the tap water from 12 other houses. Also, no organotin compounds were seen in raw water or water leaving the treatment plant, which suggested that the source was the distribution system (Sadiki et al. 1996). Other research by the same authors showed that methyltin compounds (not further specified) were detected at concentrations up to 22 ng Sn/L in distributed water samples from six municipalities in Canada (Sadiki and Williams 1996).

In the United States, dimethyltin was found to range from 0.40 to 2.2 ng Sn/L in a limited number of tap water samples from Florida in 1977 (Braman and Tompkins 1979 as cited in http://www.hc-sc.gc.ca/ewh-semt/pubs/contaminants/ps11-1sp1/non_pest_org_comp/...).

Organotins were placed on the U.S. drinking water contaminant candidate list in 1998 partly because mono- and di-organotins used in chlorinated PVC pipes were of sufficient concern to warrant further investigation (63 FR 10273). Organotins remain on the contaminant candidate list (published in February 2005), because they are known or anticipated to occur in public drinking water systems (70 FR 9071).

A risk assessment by Risk and Policy Analysts Limited, Inc. (RPA 2002, updated 2003) conducted for the European Commission evaluated the risks from organotins. In this report they provide their final conclusions regarding dimethyltin. For adult and child consumers, exposure levels from all sources, individual and cumulative, were found to be below tolerable daily intakes (TDIs). However, methyltins are imported into Europe; therefore, risks in regions that produce dimethyltins may differ.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

DMT(EHTG) and DMT(IOTG) are isomers and are considered toxicologically equivalent; therefore, data for these materials are used interchangeably.

3.1.1 Toxicokinetics, Metabolism and Distribution

In vitro Studies

Simulated Gastric Reaction

In a study designed to simulate mammalian gastric contents (0.07 M HCl), an 80:20 mixture of DMT(EHTG):MMT(EHTG) was readily converted to the chloride derivative, DMTC, under physiological conditions (pH 1-2). For the DMT(EHTG) mixture, ca. 100% of DMT(EHTG) was converted to DMTC within 0.5 hours (ORTEP Association 2000). The results of this study confirmed the use of DMTC as an appropriate surrogate for mammalian toxicology studies via the oral route.

Dermal Absorption

The absorption of an 89:11% (w/w) mixture of DMTC:MMTC was measured *in vitro* through both occluded and unoccluded human and rat epidermis (Central Toxicology Laboratory 1999a). A dose of 100 µg/cm^2 was not damaging to human epidermis. Maximum tin absorption rates were 0.015 µg/cm^2/h (occluded) and 0.006 µg/cm^2/h (unoccluded) for human epidermis, and 0.233 µg/cm^2/h (occluded) and 1.07 µg/cm^2/h (unoccluded) for rat epidermis. The percentages of applied tin absorbed were 1.4% (human, occluded), 0.25% (human, unoccluded), and 10% (rat, unoccluded and occluded). The study was conducted according to the draft OECD TG 428 for Dermal Delivery and Percutaneous Absorption: In Vitro Method.

Using the same methodology as described above, the absorption of an 80:20% (w/w) mixture of DMT(EHTG):MMT(EHTG) did not damage the human epidermis at a rate of 100 µL/cm^2 under occlusion for 24 hours (Central Toxicology Laboratory 1999b). Maximum tin absorption rates were

0.018 μg/cm^2/h (occluded) and 0.007 μg/cm^2/h (unoccluded) for human epidermis, and 2.39 μg/cm^2/h (occluded) and 1.49 μg/cm^2/h (unoccluded) for rat epidermis. The percentages of applied tin absorbed were < 0.001% (unoccluded) and 0.001% (occluded) through human epidermis, and 0.14% (unoccluded) and 0.21% (occluded) through rat epidermis. At the non-damaging concentration of 100 μL/cm^2, absorption through human epidermis is extremely slow.

In vivo Studies

DMTC, administered orally to pregnant rats at a dose of 40 mg Sn/l, was absorbed from the gastrointestinal tract of the dam and transferred across the placenta to the fetus, resulting in significantly ($p < 0.0001$) higher concentrations of tin in fetal blood (14.6 vs. 0.20 μg/g) and brain (1.17 vs. 0.32 μg/g) relative to the control (Noland et al. 1983). The T_{max} was 1 hour. The majority of tin (from DMTC) was transferred to the fetus during gestation, not during lactation. Acute inhalation toxicity studies suggest that DMTC is absorbed after inhalation exposure although the extent is not known.

Conclusion

DMTC and DMT(EHTG):MMT(EHTG) (80:20%) are not readily absorbed across the skin. DMTC (measured as Sn) administered orally to pregnant rats is transferred to the fetus during gestation.

3.1.2 Acute Toxicity

In vivo Studies

Inhalation

The acute inhalation toxicity of the dimethyltin compounds and the thioglycolate esters, EHTG and IOTG, are summarized in Table 8.

Table 8 Summary of the Acute Inhalation Toxicity of the Dimethyltin Compounds and the Thioglycolate Esters in Experimental Animals

Species	Method	Test Substance Composition	Results and Observations		Reference
DMTC					
Rat	Similar to OECD 403 with shortened duration	Not reported	Males & Females: LC50 = 125 (83.3-187.5) mg/l (125,000 mg/m^3)	1-hr aerosol exposure (3-10 micron range). Mortality: 2/10, 5/10, 7/10 and 10/10 for dose levels of 50, 100, 200 and 200 mg/L/hr. Rats exposed to lower doses experienced CNS depression. After recovery, male animals became aggressive and fought with each other. Animals were sensitive to sound and touch. Gross findings included blood in the lungs and heart failure, fluid in the chest cavity, dark spleen, and the stomach filled with gas.	Wells Laboratories 1975a
Rat	Similar to OECD 403 with shorter duration	Not reported	Males & Females: LC50 = 1632 (1285–2074) mg/m^3	1-h aerosol nose only exposure (~70% > 7 um particle size). Mortality: 0/20, 12/20 and 17/20 for dose levels of 640, 1679 and 3012 mg/m3. At 1679 mg/m3, mortalities were reported at 24 h (5 males, 1 female), 48 h (3 males, 1 female), and at 7 days (1 male, 1 female). At 3012 mg/m3, mortalities were reported at 0-1 h (2 males, 2 females), at 24 h (1 male, 2 females), at 48 h (5 males, 4 females), and at 7 days (1 male). In concentrations where mortality occurred, animals showed dyspnoea, ventral position, tremor and ruffled fur, and small hemorrhages in the lung. Symptoms became more severe with increasing dose level. All animals showed edema in the head region. Surviving animals recovered within 10-12 days. No substance-related gross changes.	Ciba-Geigy 1977

Species	Method	Test Substance Composition	Results and Observations		Reference
Rat	OECD 403 compliant	Not reported	Males & Females: LC50 = 115 (105–126) mg/m^3	4-h aerosol nose only exposure. Approximate mean particle size distribution by dose level: 44 mg/m3: 38% < 1 um, 35% 1-3 um 90 mg/m3: 45% > 7 um, 30% 1-3 um 121mg/m3: 45% 1-3 um, 20% 3-7 um, 20% > 7 um 167 mg/m3: 80% > 7 um Mortality: 0/20, 4/10, 9/10 and 20/20 for dose levels of 44, 90, 121 and 167 mg/m3. At 90 mg/m3, mortalities were reported at 0-4 h (1 each sex), 24 h (1 male), 48 h (1 male). At 121 mg/m3, mortalities were reported at 0-4 h (3 males), 24 h (1 female), 48 h (2 each sex), and at 7 days (1 female). At 167 mg/m3, mortalities were reported at 0-4 h (6 each sex), 24 h (3 each sex), and at 48 h (1 each sex). In concentrations where mortality occurred, animals showed dyspnoea, ventral position, tremor and ruffled fur, and hemorrhages in the lung. Symptoms became more severe with increasing dose level. All animals showed edema in the head region. Surviving animals recovered within 6-7 days. No substance-related gross changes.	Ciba-Geigy 1977
Rat	Similar to OECD 403 with shorter duration	Not reported	Males: LC50 = >5.8 mg/l (>5,770 mg/m^3)	1-hr. aerosol exposure. (2.5-3.5 microns). No mortality. Animals exhibited inactivity during exposure; also slight to moderate discharge around muzzle and nasal areas. Normal behavior during 14-d observations period.	Hazelton Laboratories 1976

Species	Method	Test Substance Composition	Results and Observations		Reference
Rat	Similar to OECD 403 with shorter duration	Not reported	Males: LC50 = >56.7 mg/l (>56,700 mg/m^3)	1-hr. vapor exposure. No mortalities. During exposure, all animals exhibited initial "excited" activity. Majority of exposed animals exhibited little or no activity, depression, shallow respiration, serosanguineous stains around the nose. Some rats exhibited excessive masticatory movements, preening and lacrimation, and eye squinting. Following dosing, all rats exhibited depression, shallow respiration; 8/10 animals exhibited excessive lacrimation; 9/10 exhibited wheezing. No significant gross findings.	International Bio-Research 1976
Rat	Similar to OECD 403 with shorter duration	Not reported	Males: LC50 = >16.7 mg/l (>16,700 mg/m^3)	1-hr. vapor exposure. No mortalities. Animals exhibited an initial "excited" behavior, and then little or no activity, depression, labored respiration, serosanguineous stains around the nose and/or mouth, excessive salivation, ataxia, and damp haircoat. Some rats exhibited preening, excessive lacrimation, eye squinting, and masticatory movements. No significant gross findings.	International Bio-Research 1976
DMT(IOTG)					
Rat	Hazardous Substances Labeling Act	Not reported	132 (116-149) mg/l (132,000 mg/m^3) (sex not reported)	1 hr. exposure. 48-hours post exposure rats exhibited aggressiveness and excitation (not further described). Time of death not reported. Gross findings included hemorrhages in the lungs, dark spleen and liver, and pale kidneys.	Wells Laboratories 1975b

Species	Method	Test Substance Composition	Results and Observations		Reference
Rat	OECD 403 compliant	Not reported	Males & Females: > 1968 mg/m^3	4-h nose-only aerosol exposure (predominantly > 7 microns). No female rats died during exposure or the 7-day observation period. Two male rats died at 48 hours. 24-h post treatment, rats exposed to 1968 mg/m^3 exhibited dyspnoea, lateral position, and ruffled fur. Animals that died during the study showed hemorrhages in the lungs and congested organs. Animals that survived to the end of the observation period showed no substance-related gross organ changes.	Ciba-Geigy 1974b
EHTG					
Rat	Directive 67/548/ EEC	Not reported	Males & Females: LC0 = 0.51 mg/L (510 mg/m^3)	6-h exposure. Normal body weights. No gross findings.	Epona Associates, LLC 2006a
IOTG					
Rat	Not reported	> 98% purity	Males: LC50 > 43 ppm (0.36 mg/L, 360 mg/m^3)	7-hr vapor exposure. No mortalities at 43 mg/L (room temperature) or 1710 mg/L (at 135 C). No gross findings.	Epona Associates, LLC 2006b

Conclusions**:**

Acute inhalation LC50s of the dimethyltin compounds are 115 mg/m^3 for a 4-h aerosol exposure to 125 mg/l (125,000 mg/m^3) for a 1-h aerosol exposure of DMTC, and 132 mg/l (132,000 mg/m^3) for a 1-h exposure and > 1968 mg/m^3 for a 4-h aerosol exposure of DMT(IOTG). DMT(EHTG) and DMT(IOTG) are considered toxicologically equivalent. The acute inhalation LC0 of EHTG in rats was 0.51 mg/L (510 mg/m^3) in rats for a 6-hour exposure, and the acute inhalation LC50 of IOTG in rats was 43 mg/L (43,000 mg/m^3) in rats for a 7-h vapor exposure.

Dermal

The acute dermal toxicity of the dimethyltin compounds, and the thioglycolate esters, EHTG and IOTG, are summarized in Table 9.

Table 9 Summary of the Acute Dermal Toxicity of the Dimethyltin Compounds and the Thioglycolate Esters in Experimental Animals

Species	Method	Test Substance Composition	Results and Observations		Reference
DMTC					
Rabbit	OECD 402	DMTC:MMTC (90:10)	Males & Females: LD50 = > 2000 mg/kg bw	Limit test. No mortality.	AME 1971b
Rabbit	OECD 402	DMTC:MMTC (84.8:15.2)	Males: LD50 = 380 (204–710) mg/kg bw (slope = 1.66) Females: LD50 = 413 (352–485) mg/kg bw (slope = 1.14) Both sexes: LD50 = 404 (287–568) mg/kg bw (slope = 1.48)	Patch test. Mortality: 0/10, 6/10, and 9/10 for dose levels of 200, 400, and 750 mg/kg. Time of death reported: 400 mg/kg: 3 @ 72 h, 2 @ Day 4, 1 @ Day 5; 750 mg/kg: 1 @ 48 h, 5 @ Day 4, 2 @ Day 5, 1 @ Day 9) Clinical abnormalities included slight to severe dermal irritation at site of application, urine and fecal staining, diarrhea, decreased food consumption, decreased activity, decreased defecation, tremors, wobbly gait, pale eyes, respiratory abnormalities, mucoid stools, reddened iris, convulsions, dehydration, emaciation, and raised area on the abdominal region.	Rush 1993a
DMT(EHTG)					
Rabbit	OECD 402, OPPTS 798.1100 compliant	DMT(EHTG): MMT(EHTG (70:20)	Males & Females: LD50 > 1050 mg/kg bw	Patch test. No deaths or test substance-related systemic effects. Animals showed varying degrees of skin irritation including thickened skin and chapped and flaky skin, as early as day 2 of observation; all signs of irritation had disappeared by day 12. No effects on body weight or body-weight gain were noted. No gross findings.	SRI International 1993a
DMT(IOTG)					
Rat	OECD 402 compliant	Not reported	Males & Females: LD50 > 3100 mg/kg bw	No mortalities and no symptoms of toxicity observed. No local skin irritation. No gross organ changes findings.	Ciba-Geigy 1974c
EHTG					
Rat	OECD 402	99.4% purity (undiluted)	Males & Females: LD50 > 2000 mg/kg bw	Limit test. 2/10 animals died. No cutaneous reactions. Some animals exhibited decreased activity and decreases in body weight; returned to normal during observation. No gross findings.	Epona Associates, LLC 2006a

Species	Method	Test Substance Composition	Results and Observations		Reference
IOTG					
Rat	OECD 402	99.05% purity (undiluted)	Males & Females: LD50 > 2000 mg/kg bw	Semi-occlusive patch test (limit test). No skin irritation; no changes in general behavior or body weight gain.	Epona Associates, LLC 2006b
Rabbit	OECD 402 compliant	> 98% purity	Males & Females: LD50 > 5000 mg/kg bw	Limit test.	Epona Associates, LLC 2006b

Conclusions:

DMTC

The acute dermal LD50s of the dimethyltin compounds are 380–413 mg/kg bw and > 2000 mg/kg bw for DMTC, > 1050 mg/kg bw for DMT(EHTG), and > 3100 mg/kg bw for DMT(IOTG). The acute dermal LD50 of EHTG is > 2000 mg/kg bw, and the acute dermal LD50s of IOTG are > 2000 mg/kg bw in rats, and > 5000 mg/kg in rabbits.

Oral

The acute oral toxicity of the dimethyltin compounds and the thioglycolate esters, EHTG and IOTG, are summarized in Table 10.

Table 10 Summary of the Acute Oral Toxicity of the Dimethyltin Compounds and the Thioglycolate Esters in Experimental Animals

Species	Method	Test Substance Composition	Results and Observations		Reference
DMTC					
Rat	OECD 401 compliant	DMTC: MMTC:TMTC (84.8:15.2 0.05) (ca. 50% in water)	Males: LD50 = 546 (282–1057) mg/kg bw Females: LD50 = 328 (209–516) mg/kg bw Both sexes: LD50 = 409 (305–547) mg/kg bw	Mortality: 0/10, 4/10, and 6/10 for dose levels of 200, 300 and 500 mg/kg bw. Death occurred 2-4 days following dosing at 300 mg/kg, and within 24 hours at 500 mg/kg. Dose-dependent reduction in mean body weight for females. Clinical abnormalities included decreased activity, salivation, rough haircoat, mucoid/soft stools, fecal and urine staining, hunched posture, dehydration, decreased defecation and food consumption, gasping, and rales. Gross necropsy findings included dark red medulla of the kidney, dark red foci on the thymus, mottled lungs, abnormal colored mucoid/fluid contents, reddened mucosa, and dark red linear striations on the stomach.	Elf Atochem NA 1993[1]
Rat	OECD 401 compliant	Not reported	Males: LD50 = 73.86 (64.4–84.7) mg/kg bw	Mortality: 1/10, 2/10, 5/10, 6/10, 8/10, 8/10 and 10/10 for dose levels of 48, 57, 69, 83, 100, 120 and 144 mg/kg bw. Within 2-3 hours of dosing, animals exhibited lassitude, hypokinesia, lack of appetite, thirst, unkempt fur, general weakness, a tendency to lay on their sides, and death within 24-72 hours of treatment.	Klimmer 1971
Rat	OECD 401 compliant	Not reported	Males: LD50 = 141.4 (100.2–196.1) mg/kg bw	Mortality: 1/6, 5/6, 6/6, 6/6 and 6/6 for dose levels of 100, 200, 400, 800 and 1600 mg/kg bw. Time of death reported: 200 mg/kg: 1 @ 8-24 hrs, 2 @ 48 hrs, 1 @ 72 hrs, 1 @ day 21; 400 mg/kg: 4 @ 8-24 hrs, 2 @ 72 hrs; 800 mg/kg: 5 @ 8-24 hrs, 1 @ 96 hrs; 1600 mg/kg: 6 @ 8-24 hrs. Within 8-24 hours of dosing, animals exhibited depression, convulsions and death at 200 mg/kg and higher. No significant gross autopsy findings.	AME 1971a

Species	Method	Test Substance Composition	Results and Observations		Reference
DMT(EHTG)					
Rabbit	OECD 401	Undiluted	Males & Females: LD50 = 1150 (850–1550) mg/kg bw	Mortality: 0/10, 4/10, 5/10, and 10/10 for dose levels of 625, 880, 1250 and 2500 mg/kg bw. Time of death reported: 880 mg/kg: 2 @ 24 hrs, 2 @ 48 hrs; 1250 mg/kg: 4 @ 24 hrs, 1 @ 48 hrs), 2500 mg/kg: all died within 24 hrs. Clinical signs during observation included varying degrees of depression, comatose, piloerection, eye squinting, hunched posture, labored breathing, ataxia, diarrhea, fecal and urine stains, emaciation, and unkempt fur coat. All animals exhibited body weight gain on day 14, with the exception of one male (1250 mg/kg bw).	Morton International 1996a
Rat	16 CFR 1500	Not reported	Males: LD50 = 1710 (1260–2330) mg/kg bw	Mortality: 0/5, 0/5, 4/5, 5/5 and 5/5 for dose levels of 464, 1000, 2150, 4640 and 10,000 mg/kg bw. Time of death reported: 2150 mg/kg: 4 within 72 hours; 4640 and 10,000 mg/kg: all died within 24 hrs. Clinical signs included diarrhea, hunched posture, hyperactivity, depression, piloerection, ataxia, and emaciation. Gross necropsy results for animals that died during observation included moderate autolysis, mottled livers, thin-walled stomachs containing green-yellow material, irritated intestines, pale and congested kidneys, darkened and mottled lungs, and staining around the mouth. No gross finding in animals that survived to the end of the study.	Hill Top Research 1984

Species	Method	Test Substance Composition	Results and Observations		Reference
DMT(IOTG)					
Rat	OECD 401 compliant	Diluted in CMC	Males & Females: LD50 = 1214 (1015–1453) mg/kg bw	Mortality: 0/10, 3/10, 8/10 and 10/10 for dose levels of 600, 1000, 1670 and 2150 mg/kg bw. Time of death reported: 1000 mg/kg: 1 @ 24 hrs, 2 on Day 7; 1670 mg/kg: 6 died @ 24 hrs, 1 @ 48 hrs, 1 on Day 14; 2150 mg/kg: 5 @ 24 hrs, 5 on Day 14). Within 24 hours after treatment, rats in all dose groups showed sedation, dyspnoea, exophthalmus, curved position, ataxia, and ruffled fur. Symptoms increased in severity with increasing dose level. No gross findings.	Ciba-Geigy 1974a[1]
Rat	Compliant with Federal Hazardous Substances Act	Undiluted	Males & Females: LD50 = 1090–1735 mg/kg bw	Mortality: 0/10, 0/10, 4/10, 9/10, and 10/10 for dose levels of 0.215, 0.464, 1.00, 2.15, and 4.64 ml/kg. Time of death reported: 1.00 ml/kg: 3 @ 24 hrs, 1 @ 48 hrs; 2.15 ml/kg: 2 @ 24 hrs; 7 @ 48 hrs; 4.64 ml/kg: 1 @ 6 hrs, 9 @ 24 hrs. Symptoms of systemic toxicity included depression, depressed righting and placement reflexes, labored respiration, diarrhea, bloody-appearing stains around nose and/or mouth, urine stains, excessive salivation, piloerection, unkempt fur , and mortality.	Hill-Top Toxicology 1978
EHTG					
Rat	OECD 401 compliant	> 98% purity	Males: LD50 = 303 (259-355) mg/kg bw Females: LD50 = 334 (250-446) mg/kg bw	Body weights were unaffected. No gross findings. No significant damage to liver or kidneys.	Epona Associates, LLC 2006a
Mouse	OECD 401 compliant	> 98% purity	Males: LD50 = 1800 (1600-2020) mg/kg bw Females: LD50 = 1510 (1410-1630) mg/kg bw	Not reported.	Epona Associates, LLC 2006a
Guinea pig	OECD 401 compliant	> 98% purity	Males: LD50 = 955 (743-1230) mg/kg bw Females: LD50 = 1120 (888-1420) mg/kg bw	Not reported.	Epona Associates, LLC 2006a

Species	Method	Test Substance Composition	Results and Observations		Reference
IOTG					
Rat	OECD 401 compliant	> 98% purity	Females: LD50 = 485 (281-833) mg/kg bw	Mortality: 0/5, 0/5, 3/5, 5/5, 5/5 and 5/5 for dose levels of 126, 252, 500, 1000, 2000 and 3980 mg/kg.	Epona Associates, LLC 2006b

Conclusion:

The acute oral LD50s of the dimethyltin compounds are 74–546 mg/kg bw in rats for DMTC, . 1150 and 1710 mg/kg bw in rats for DMT(EHTG), and 1090–1735 mg/kg bw in rats for DMT(IOTG). Acute oral LD50s of EHTG are 303–334 mg/kg bw in rats, 1510–1800 mg/kg bw in mice, and 955–1120 mg/kg bw guinea pigs, and the acute oral LD50 of IOTG is 485 in rats.

3.1.3 Irritation

Skin and eye irritation studies of DMTC and DMT(EHTG)/(IOTG) are summarized in Table 11. Data for the thioglycolate esters EHTG and IOTG are also included in the table.

Table 11 Summary of Irritation Studies of the Dimethyltin Compounds and the Thioglycolate Esters

Compound	Species	Test Substance Composition	Method	Results and Observations	Reference
Irritation (skin)					
DMTC	Rabbit	DMTC: MMTC (84.8:15.2)	OECD 404	Semi-occlusive patch test. Corrosive. No mortality. Blanching and necrosis with severe edema on 6/6 sites within 1 hr of application. Eschar formation on 3/6 sites at termination.	Rush 1993b
DMTC	Rabbit	Not reported	Draize test	Moderate to severe erythema and eschar formation at intact and abraded site at 24 and 72 hrs. Very slight edema at 24 hours. No edema at 72 hours.. PDII = 1.75	AME 1971c
DMT(EHTG)	Rabbit	Undiluted	16 CFR 1500 (Draize)	Occlusive patch test. Slight to moderate edema; slight to well-defined erythema. No corrosive tissue damage. PDII = 2.6	Hill Top Research 1984
DMT(EHTG)	Rabbit	Undiluted	U.S. AFDO (1959)	2/3 females died post treatment. At 48 hours, all animals exhibited tremors, slight asynchronisms of the extremities, and curved posture. Animals that died had refused food. Very slight to moderate erythema and very slight edema. PDII = 1.5	Ciba-Geigy 1974d
DMT(IOTG)	Rabbit	DMT(IOTG): MMT(IOTG) (95:5%) Undiluted	Federal Hazardous Substances Act	Very slight to well-defined erythema and very slight or slight edema at intact and abraded skin sites at 24 h; erythema and edema persisted at the majority of sites at 72 h.	Hill Top Research 1971
EHTG	Rabbit	Undiluted (99.4% purity)	OECD 404	Erythema: mean scores at 24, 48, and 72 hours were 1.3, 1.7, and 1.3 (reversed by day 6). Edema: mean scores at 24, 48, and 72 hours were 0.0, 0.0, and 0.3 (reversed by day 3). No necrosis noted.	Epona Associates, LLC 2006a
IOTG	Rabbit	Undiluted (99.05% purity)	OECD 404	Erythema: mean scores at 24, 48, and 72 hours were 1.0, 1.7, and 1.7. Edema: mean scores at 24, 48, and 72 hours were 0.0. Moderate cutaneous reactions; no necrosis.	Epona Associates, LLC 2006b

Compound	Species	Test Substance Composition	Method	Results and Observations	Reference
Irritation (eye)					
DMTC	Rabbit	Undiluted	Federal Hazardous Substances Labeling Act	Instillation of the test substance into the eye caused pain. 1 h after application there was partial corneal destruction. The opacity of the cornea was such that the iris was not visible in 3 animals and partly obscured in 1 animal. Marked chemosis of the conjunctivae in all animals. Loss of sensation to touch over the cornea in 5/6 animals. After 6 h, all animals appeared lethargic and had severe chemosis with blood stained discharge from the eyes, with completely opaque cornea in 5/6 animals. Phylctenar occurred on the cornea of 1 animal. Conjunctival mucosa of all rabbits was necrotic. At 24 hours, moderate to severe necrosis of conjunctivae was present in all animals with severe periorbital edema.	Drake 1973
DMTC	Rabbit	Undiluted	Not reported	Severe irritation and complete enucleation of the eye in the treated animals. Group mean scores at 24, 48 and 72 hours were 110/110.	Affiliated Medical Enterprises, Inc. 1971
DMT(EHTG)	Rabbit	Undiluted	U.S. AFDO (1959)	2/3 females died within 3 days of application. PEII = 0 (iris), 0 (conjunctivae), 0.4 (cornea)	Ciba-Geigy 1974e
DMT(EHTG)	Rabbit	Undiluted	16 CFR 1500	Slight conjunctival erythema observed in 3 animals between 24 and 48 hours after application. No positive test scores for any of the test animals.	Hill Top Research 1984
DMT(IOTG)	Rabbit	DMT(IOTG): MMT(IOTG) (95:5%) Undiluted	Federal Hazardous Substances Act	No irritative effects were observed involving the cornea, iris or conjunctivae at any time during the study.	Hill Top Research 1971
EHTG	Rabbit	Undiluted (99.4% purity)	OECD 405	Not irritating. No ocular reactions observed.	Epona Associates, LLC 2006a
EHTG	Rabbit	Undiluted (> 98% purity)	Not reported	Slightly irritating. Slight reddening of the conjunctiva (recovery after 8 hours).	Epona Associates, LLC 2006a
EHTG	Rabbit	50% dilution (> 98% purity)	Not reported	Not irritating.	Epona Associates, LLC 2006a
IOTG	Rabbit	Undiluted (99.05% purity)	OECD 405	Slightly irritating. Slight chemosis and/or redness of the conjunctiva noted within 24 hours post treatment.	Epona Associates, LLC 2006b

Compound	Species	Test Substance Composition	Method	Results and Observations	Reference
IOTG	Rabbit	Undiluted (> 98% purity)	Not reported	Slightly irritating. Very slight pain and possible conjunctival inflammation immediately after instillation. No signs of irritation or injury during observation period.	Epona Associates, LLC 2006b

Conclusions:

DMTC

DMTC is a corrosive to the skin and eyes.

DMT(EHTG)/(IOTG)

DMT(EHTG)/(IOTG) are slightly to moderately irritating to skin and minimally to not irritating to eyes

EHTG/IOTG

EHTG and IOTG are slightly irritating to the skin. EHTG has no to slight eye irritation potential, similar signs of eye irritation are seen with IOTG.

3.1.4 Sensitization

Sensitization studies of the dimethyltin compounds and selected thioesters are summarized in Table 12.

Table 12 Summary of Sensitization Studies of the Dimethyltin Compounds and the Thioglycolate Esters

Compound	Species	Test Substance Composition	Method	Result and Observations	Reference
DMTC	Guinea pig	0.1% in polyethylene glycol	Maurer optimization test	Erythema: Scored 0.5-1 in all but one animal (scored 2). Dermal reactions similar during induction. No delayed-type sensitization observed.	Davis and Elliott 1973
DMT(EHTG)	Guinea pig	0.1% in saline	Maurer optimization test	Weak sensitizer. Erythema scores: 4/10 males and 7/10 females scored 1.	Ciba-Geigy 1975
DMT(EHTG)	Guinea pig	50% in acetone	Buehler test	No sensitization observed.	Hill Top Biolabs, Inc. 1989
DMT(IOTG)	Guinea pig	0.1% in saline	Maurer optimization test	Weak sensitizer. Sensitization rate was 55% (11/20 animals). Erythema (Draize) score was 0-1 in males and females.	Ciba-Geigy 1975
EHTG	Guinea pig	Induction: 25% in paraffin oil Challenge: Undiluted	OECD 406	Sensitizing. Well defined erythema of 10/20 and 5/20 treated animals at 24 and 48 hours. No edema noted.	Epona Associates, LLC 2006a
IOTG	Guinea pig	Induction: 25% in paraffin oil Challenge: Undiluted	OECD 406	Ambiguous. Slight cutaneous reactions attributed to a slight irritant potential observed in 1 control animal and 4 treatment animals. Well defined erythema of 3/20 and 5/20 treated animals at 24 and 48 hours. No edema noted.	Epona Associates, LLC 2006b

Conclusions:

DMTC

No sensitization potential.

DMT(EHTG)/(IOTG)

No to slight sensitization potential.

EHTG/IOTG

No to slight sensitization potential.

"The GPMT of Magnusson and Kligman, which uses adjuvant, and the non-adjuvant Buehler test are given preference over other methods." This perception is shared in other National guidelines.

The barely perceptible erythema responses in the Maurer Test with the DMT(EHTG) cannot be considered a definitive indication of a response when the Buehler test with the same compound is negative. However, the conclusions supported by the data in the table above are that DMT(EHTG) is positive, but equivocally so, for sensitization and DMTC is not a sensitizer.

3.1.5 Repeated Dose Toxicity

Studies in Animals

Oral

Dimethyltin dichloride

Data from two 90-day studies are summarized in Table 13.

Table 13 Summary of 90-day repeated dose oral toxicity of DMTC

Method	Dose level	Results and Observations	Reference
Similar to OECD 408	25 ppm in drinking water (1.6 and 2.2 mg/kg bw/day for males and females, respectively)	(LOAEL) Treatment-related effects reported: • Decreased food consumption (g/animals) for males ($p < 0.05$, $p < 0.01$ or $p < 0.001$) • Decreased water consumption (both sexes) during treatment ($p < 0.05$ or $p < 0.01$) • Biochemical changes, including a slight decrease in albumin levels in females (3.2 vs. 3.5 g/dL) ($p < 0.05$) • Neuropathological lesions (vacuolization in the brain and spinal cord tissue at terminal evaluation) (both sexes) • Absolute organ weight changes at terminal sacrifice, including increased kidneys weight in females (2.1 vs. 1.8 g) ($p < 0.05$) • Relative organ weight changes at terminal sacrifice, including increased kidneys weight in females (0.70 vs. 0.61 g) ($p < 0.05$)	ClinTrials BioResearch 1997
	75 ppm in drinking water (5.2 and 6.7 mg/kg bw/day for males and females, respectively)	Treatment-related effects reported: • Mortality (1 male) • Decreased food consumption (g/animals) for males ($p < 0.05$, $p < 0.01$ or $p < 0.001$) • Decreased water consumption (both sexes) during treatment ($p < 0.05$ or $p < 0.01$) • Decreased body weights (males) ($p < 0.05$ or $p < 0.01$) • Reduced total motor activities in females ($p < 0.01$ or $p < 0.001$) • Biochemical changes, including decreased total protein (5.8 vs. 6.2 g/dL) in females ($p < 0.05$); decreased albumin in females (3.2 vs. 3.5 g/dL) ($p< 0.01$) • Absolute organ weight changes at terminal sacrifice, including decreased thymus weights in males (0.17 vs. 0.24 g) ($p < 0.05$); decreased heart weight (1.58 vs. 1.83 g) ($p < 0.05$); increased kidneys weight in females (2.3 vs. 1.8 g) ($p < 0.01$) • Relative organ weight changes at terminal sacrifice, including decreased thymus weights in males (0.035 vs. 0.046 g) ($p < 0.05$); increased kidney weights in females (0.74 vs. 0.61 g) ($p < 0.01$) • FOB findings, including decreased body temperature ($p < 0.05$) in females; ataxia and unusual hindlimb movements in 1 male • Vacuolization of the brain (1 male, 3 females) and spinal cord (1 female) • Small thymus in males • Lymphoid atrophy	

Method	Dose level	Results and Observations	Reference
	200 ppm in drinking water (15.5 and 19.4 mg/kg bw/day for males and females, respectively)	Terminated for excessive mortality. Treatment-related effects reported: • Decreased food consumption (g/animals) (both sexes) ($p < 0.05$, $p < 0.01$ or $p < 0.001$) • Decreased water consumption (both sexes) during treatment ($p < 0.05$ or $p < 0.01$) • Decreased body weights (both sexes) ($p < 0.05$ or $p < 0.01$) • Biochemical changes, including increased BUN (25.9 vs. 15.1 mg/dL) in males ($p < 0.01$); slight increase in creatinine (0.8 vs. 0.7 mg/dL) in males ($p < 0.05$); increased phosphorus in males (9.52 vs. 8.28 mg/dL) ($p < 0.05$); decreased potassium (3.73 vs. 4.72 meq/L) ($p < 0.01$) • FOB findings, including ataxic gate, tremors, and clonus of jaws in 1 male; tremors and clonic convulsions in 3 females; hunched poster in 1 male; and ataxia and red liquid material around urogenital region in 1 female. • Nervous system lesions of the brain and spinal cord in preterminal animals characterized by ventricular dilatation, neuronal necrosis, and white matter vacuolization. • Small thymus (males) and/or spleen, emaciated carcass, dilatation of digestive tract/discolored digestive material, and dark areas on the stomach and/or lungs in preterminal animals	
OECD 408	1 ppm diet (0.06 and 0.07 mg/kg/day for males and females, respectively)	No treatment-related effects observed.	TNO 1999
	6 ppm diet (0.39 and 0.41 mg/kg/day for males and females, respectively)	No treatment-related effects observed.	
	15 ppm diet (0.98 and 1.02 mg/kg/day for males and females, respectively)	(NOAEL) No treatment-related effects observed.	

Method	Dose level	Results and Observations	Reference
	200 ppm diet (16.81 and 17.31 mg/kg bw/day for males and females, respectively)	(LOAEL) Terminated for excessive mortality. Treatment-related effects reported: • Small thymus and/or spleen (females) • Submeningeal edema in the brain (7/10 males) ($p < 0.01$), 4/10 females (not statistically significant in females) • Multifocal cell death (brain) 10/10 males and 10/10 females ($p < 0.001$) • Cortical tubular dilatation in the kidneys (9/10 males ($p < 0.001$) and 5/10 females ($p < 0.05$) • Decreased brown pigment accumulation in the spleen (10/10 males, 10/10 females) ($p < 0.001$) • Corticomedullary hemorrhages in the thymus of 4/9 females ($p < 0.05$) • Slight to severe cortical lymphoid depletion in the thymus (6/9 females) ($p < 0.01$) • Neuronal death in the hippocampal region (both sexes) ($p < 0.05$ and $p < 0.01$), the tenia tecta (4/5 females) ($p < 0.05$), the entorhinal cortex (5/5 females) ($p < 0.001$), the perirhinal cortex (5/5 females) ($p < 0.01$), the piriform cortex (6/6 males, 5/5 females) ($p < 0.01$), and in the amygdale (4/6 males – not significant, and 5/5 females) ($p < 0.01$) • Single cell neuronal death in the perirhinal cortex (5/6 males) ($p < 0.05$) • Single cell neuronal death in the neocortical area (5/5 females) ($p < 0.01$), • Severe neurological and neurobehavioral signs (tremors, convulsions, increased footsplay, hunched posture), • No treatment-related effects to reproductive tissues and organs.	

The 13 week **drinking water study** in rats with DMTC used a mixture (DMTC:MMTC; 90:10%). There was a control group and 3 treatment groups (15/sex/group in the main study and 15/sex/group in the neurotoxicity component) at doses of 25, 75, and 200 ppm (equivalent to 1.6-2.2, 5.2-6.7, and 15.5-19.4 mg/kg/day, respectively). Body weights and food consumption were measured weekly while water consumption and clinical signs were recorded daily.

An interim gross necropsy was conducted after 4 weeks of exposure on 5 rats/sex/group (in 200 ppm group, only males were tested) that included organ weight measurements. A full histopathological evaluation was performed on animals in the control and 75 ppm dose groups, and a limited histopathological evaluation was conducted on rats in the 25 ppm group. All remaining surviving animals from the 25 and 75 ppm groups (10/sex) were subjected to gross necropsies and organ weight measurements at the end of the 13-week exposure period. Hematology, blood biochemistry, and urinalysis parameters were measured during the course of the study.

Neurotoxicity component: After 13-weeks of exposure, 5 rats/sex from the control, 25 ppm, and 75 ppm groups received whole-body perfusions. A complete neuropathological examination was conducted on animals in the control and 75 ppm groups, while a limited examination (brain and spinal cord only) was conducted on animals in the 25 ppm group.

At the end of the 13-week treatment period, all remaining animals were removed from treatment for two weeks and a Functional Observation Battery (FOB) was performed. Following the recovery phase, partial gross necropsies (limited to the nervous system) were performed on 5 animals/sex/treatment group. All remaining recovery animals received complete gross pathological examinations (excluding the nervous system).

At 200 ppm (equivalent to 15.5 and 19.5 mg/kg/day for males and females, respectively) death, reduced body weight, and decreased food and water intake were observed, as well as blood biochemical changes, behavioral effects, neuropathological lesions, and reduced thymus weight in males. All rats at 200 ppm either died or were sacrificed due to poor condition by Week 6. Clinical signs of neurotoxicity observed in these animals included tremors and convulsions. At 75 ppm (equivalent to 5.2 and 6.7 mg/kg/day for males and females, respectively) one male died, male body weights were reduced, food and water intake were decreased, motor activity was reduced (females only), and neuropathological lesions were observed. Clinical signs of neurotoxicity observed at 75 ppm also included tremors and convulsions. At the low dose or 25 ppm (equivalent to 1.6 and 2.2 mg/kg/day for males and females, respectively) no deaths occurred. Treatment-related findings at 25 ppm included reduced food (males only) and water intake and neuropathological lesions.

A histopathological evaluation was performed on the reproductive tissues and organs. No treatment-related changes or pathological findings were observed in the ovaries, epididymis, testes, uterus, vagina, or seminal vesicles in the DMTC-treated animals.

The no-observed-adverse-effect level (NOAEL) was considered to be less than 25 ppm (<1 .6 and < 2.2 mg/kg/day for males and females, respectively).

The 13 week **dietary study** in rats with DMTC used a mixture [DMTC:MMTC; 63.5:33.5%]. There were 4 treatment groups plus one control group of male and female animals (10/sex/group). Satellite groups of 6 rats per sex per treatment level were run concurrently for neuropathological evaluations. Test material was incorporated into basal diet at concentrations of 0, 1, 6, 15, and 200 ppm (equivalent to 0.06-0.07, 0.39-0.41, 0.98-1.02, and 16.8-17.3 mg/kg/day in males and females, respectively). Individual body weights were measured weekly throughout the study. Feed consumption was measured per cage on a weekly basis. Neurobehavioural testing (FOB and motor activity) was conducted prior to study initiation, and on weeks 1, 4, 8, and 13. These evaluations were conducted on 4 rats/sex from each of the main groups and on all animals in each of the satellite groups. Blood hematology and clinical chemistry parameters were measured for all surviving rats of the main groups at necropsy. Urinalysis and a renal concentration test were conducted on days 87 and 88 for all surviving rats in the main groups. Following the 13-week treatment period gross necropsies were conducted on all surviving animals from the main groups. Histopathological examinations were performed on tissues and organs collected from animals in the main control group, the main 15 ppm group, the main 200 ppm group and all animals which died during the study. All surviving animals from satellite groups were subjected to whole body perfusion fixation. Relevant tissues were collected from these animals for neuropathological evaluations including the brain, spinal cord, sciatic nerve, tibial nerve, sural nerve, and plantar nerve.

Neurotoxic effects of the test substance became evident in high dose animals (200 ppm) after one month of treatment. Three high dose females died and a number of high dose animals of both sexes started to develop signs of neurotoxicity including tremors and convulsions. Mean body weights were reduced for high dose males as well as food consumption values for both sexes. Histopathological treatment-related changes observed at 200 ppm included changes in the brain, kidneys, and thymus. The effect on the thymus was not considered a direct toxic effect, but an effect caused by stress, due to the severe effects of the test substance. Females in the high dose group (200 ppm) had an increased incidence of corticomedullary hemorrhage in the thymus, and most high-dose females showed cortical lymphoid depletion in the thymus.

A histopathological evaluation was done on reproductive tissues and organs. Microscopic observations of the reproductive tissues and organs found no abnormalities in the mammary glands or testes, perivascular mononuclear cell infiltrate in the epididymides in 1/10 males in the 15 ppm dose group and 4/10 males in the control group, focal mineralization in the ovaries of 6/10 females (15 ppm) and 2/10 females (control), ovarian cysts in 1/10 females (15 ppm) and 3/10 females

(control), and luminal dilatation in the uterus of 2/10 females at 15 ppm, 1/1 females at 6 ppm, and 1/10 females in the control group. None of these changes were statistically significant.

Neuropathological treatment-related findings observed at 200 ppm included pathological changes in several parts of the brain (neuronal death). No treatment-related effects were observed at any other dose level up to and including 15 ppm.

The no-observed-adverse-effect-level (NOAEL) was 15 ppm. This was equivalent to 0.98 (males) and 1.02 (females) mg of MMTC/DMTC (30/70) per kg body weight per day.

Table 14 Summary of 90-day Drinking Water and Dietary Studies of DMTC

Drinking Water Study 90:10 dimethyltin:methyltin chloride	**Feeding Study** 66.5:33.5 dimethyltin:methyltin chloride
NOAEL < 25 ppm	NOAEL = 15 ppm (0.98 and 1.02 mg/kg/day for males and females, respectively)
LOAEL = 25 ppm (1.6 and 2.2 mg/kg/day for males and females, respectively)	LOAEL = 200 ppm (16.81 and 17.31 mg/kg/day for males and females, respectively)

Since the studies used mixtures of different proportions, a more directly comparable value is the dose based on the percentage of DMTC, which is anticipated to be more potent that MMTC. The dose levels (total DMTC) consumed, in mg/kg/day, were:

Table 15 Dose Levels (Total DMTC) Consumed in 90-day Studies

Drinking Water Study	**Feeding Study**
Males: 25 ppm: 1.42 mg/kg/day (LOAEL for neuropathology) 75 ppm: 4.63 mg/kg/day 200 ppm: 13.8 mg/kg/day (terminated for excess mortality)	Males: 1 ppm: 0.04 mg/kg/day 6 ppm: 0.26 mg/kg/day 15 ppm: 0.62 mg/kg/day (NOAEL for neuropathology) 200 ppm 11.18 mg/kg/day (terminated for excess mortality)
Females: 25 ppm: 1.96 mg/kg/day (LOAEL for neuropathology) 75 ppm: 5.96 mg/kg/day 200 ppm: 17.26 mg/kg/day (terminated for excess mortality)	Females: 1 ppm: 0.05 mg/kg/day 6 ppm: 0.27 mg/kg/day 15 ppm: 0.65 mg/kg/day (NOAEL for neuropathology) 200 ppm: 11.51 mg/kg/day (terminated for excess mortality)
NOAEL < 25 ppm LOAEL = 25 ppm (1.6 and 2.2 mg/kg/day for males and females, respectively)	NOAEL = 15 ppm (0.98 and 1.02 mg/kg bw/day in males and females, respectively) LOAEL = 200 ppm (16.81 and 17.31 mg/kg/day for males and females, respectively)

DMT(EHTG)/(IOTG)

There are no available data for this compound; however, data from the gastric hydrolysis studies indicated that DMT(EHTG) hydrolyzes rapidly to DMTC and EHTG. Thus, toxicity of DMT(EHTG) can reasonably be extrapolated on a qualitative and quantitative basis from the repeated oral dose toxicity results for DMTC, taking into consideration the differences in molecular weight of the two materials. Neurotoxicity would be predicted to be the critical toxic effect for DMT(EHTG). An estimate of the NOEL for DMT(EHTG) could be based on the 1 mg/kg/d NOAEL in the 90-day feeding study with DMTC .

EHTG

A 28-day oral study of EHTG indicates that administration of up to 0.2% in the diet of rats did not lead to any treatment-related effects. The NOAEL in this dietary study was 0.2 %, equivalent to 168 mg/kg-bw/day for males and 173 mg/kg bw/day for females (BIBRA 1988 cited in Epona Associates, LLC 2006a).

IOTG

A 14-day inhalation study of IOTG indicates that administration of 3.2 ppm (NOAEL) did not lead to any treatment-related effects (Yakel and Kociba 1979 cited in Epona Associates, LLC 2006b).

Conclusion

The two oral 90-day studies provide a complete toxicological profile of DMTC. Neurotoxic effects were seen in at all dose levels in the drinking water study and this study did not demonstrate a NOAEL. Of the two studies only the dietary study fulfills all of the guideline requirements. The NOAEL from the dietary study was approximately 1 mg/kg/day. The critical toxic effect in both studies was neurotoxicity; tremors and convulsions were observed in a dose-related manner. Histopathology (feed study) confirmed neuronal death in the cerebellum and lesions in the hippocampal region, the piriform, entorhinal, and perirhinal cortices, the amygdala, the olfactory nuclei and the tenia tecta. The NOAEL was 15 ppm (feed; ~1 mg/kg/day) and the LOAEL was 25 ppm (water; ~2.2 mg/kg bw/day).

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

The *in vitro* genetic toxicity of the dimethyltin compounds and thioglycolate esters is summarized in Table 16.

Table 16 Summary of In Vitro Genotoxicity Studies of the Dimethyltin Compounds and Thioglycolate Esters

Type of Test (Method)	Test System (Strains Tested)	Dose	Result	Reference
DMTC				
Bacterial reverse mutation assay (OECD 471)	*Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538); conducted with and without metabolic activation	Up to 5000 µg/plate (first assay); up to 1000 µg/plate (second assay)	Negative	Morton International 1990a
Bacterial reverse mutation assay (OECD 472)	*Escherichia coli* (WP2 *uvr*A); conducted with and without metabolic activation	Up to 5000 µg/plate	Negative	Morton International 1990b
Bacterial reverse mutation assay (Nohmi et al. 1986 – modified Ames)	*Salmonella typhimurium* (TA100); conducted without metabolic activation	Up to 10 µg/tube	Positive	Hamasaki et al. 1993
HGPRT assay (OECD 476)	Chinese Hamster ovary cells (CHO-K1); conducted with and without metabolic activation	Up to 150 µg/ml	Negative	Morton International 1990c
Chromosomal aberration test (OECD 473)	Human peripheral lymphocytes; conducted with and without metabolic activation	Up to 160 µg/ml	Positive w/activation Negative w/o activation	Morton International 1990d
SOS chromotest (Quillardet and Hofnung 1985)	*Escherichia coli* (PQ37); conducted without metabolic activation	Up to 100,000 µg/tube	Negative	Hamasaki et al. 1992
Rec-assay (Kada et al. 1980)	*Bacillus subtilis* (H17 Rec^+ and M45 Rec^-); conducted without metabolic activation	Up to 100,000 µg/50 µl	Positive	Hamasaki et al. 1992
DMT(EHTG)/(IOTG)				
Bacterial reverse mutation assay	*Salmonella typhimurium* (TA98, TA100, TA102, TA1535, TA1537) and *Escherichia coli* (WP2 *uvr*A); conducted with and without metabolic activation	Up to 5000 µg/plate	Negative	Morton International 1996b
EHTG				
Bacterial reverse mutation assay (OECD 471)	*Salmonella typhimurium* (TA98, TA100, TA102, TA1535, TA1537); conducted with and without metabolic activation	Up to 4000 µg/plate	Negative	Epona Associates, LLC 2006a
IOTG				
Bacterial reverse mutation assay (OECD 471)	*Salmonella typhimurium* (TA98, TA100, TA102, TA1535, TA1537); conducted with and without metabolic activation	Up to 5000 µg/plate	Negative	Epona Associates, LLC 2006b

Conclusion

DMTC, DMT(EHTG)/(IOTG), and the thioesters, EHTG and IOTG, were not mutagenic in standard Ames assays using multiple strains of *Salmonella typhimurium* conducted with and without metabolic activation. DMTC also was negative in an Ames test using *Escherichia coli,* an HGPRT assay and an SOS chromotest conducted with and without metabolic activation. DMTC was positive (with activation) and negative (without activation) in an assay for chromosomal aberrations (OECD TG 473), positive in a modified bacterial reverse mutation assay with *S. typhimurium strain* TA100 conducted without activation, and positive in a Rec-assay without activation.

No data on the *in vitro* genetic toxicity of DMT(IOTG) were located; however, data from DMT(EHTG) provides information for this endpoint (Refer to Section 1.5 for analogue discussion).

In vivo Studies

DMTC

In a mouse micronucleus assay (ASTM Standard No. E 1263-88), DMTC (> 99% purity), at oral levels up to 400 mg/kg bw, did not increase the number of polychromatic erythrocytes (PE) or the ratio of micronucleated PE to RNA-positive erythrocytes in the dosed animals (Morton International 1991). Doses of 0, 100, 200 and 400 mg DMTC/kg bw administered 24, 48 or 72 hours prior to sacrifice yielded a percentage of PCE with micronuclei of 0.24% or less in males, and 0.25% of less in females; the positive control, urethane (300 mg/kg bw in deionized water), yielded 2.43%, 1.29% and 0.65% PCE with micronuclei, respectively, for the same time intervals.

In an unscheduled DNA synthesis bioassay, DMTC (purity not reported), at oral levels up to 225 mg/kg bw, was not genotoxic in male rat hepatocytes (SRI International 1993b). Doses of 0, 50, 110 and 225 mg DMTC/kg bw yielded values for mean net grains per nuclei of less than 0 (-8.9 to -6.1) and percentages of cells in repair of < 5% (0-2%). The positive control, dimethyl nitrosamine, yielded a value of 28.4 for mean net grains per nuclei and a percentage of cells in repair of 93%.

DMT(EHTG)/(IOTG)

There is no available *in vivo* genotoxicity information for DMT(EHTG) or DMT(IOTG), however, data from the mouse micronucleus tests of DMTC and the ligand, EHTG, were negative and are representative of DMT(EHTG)/(IOTG) for this endpoint (Refer to Section 1.4 for category justification).

EHTG/IOTG

In a mouse micronucleus assay (OECD TG 474), EHTG (> 09.9% purity), at dose levels up to 900 mg/kg bw, did not increase the mitotic index or the PCE/NCE ratio in the dosed animals (BioReliance 1998 cited in Epona Associates, LLC. 2006a). No data on the *in vivo* genetic toxicity of IOTG are available; however, data from the mouse micronucleus test of EHTG are representative of IOTG for this endpoint.

Conclusion

DMTC, DMT(EHTG), EHTG, and IOTG were negative in standard Ames tests, with and without metabolic activation. DMTC and EHTG were negative in *in vivo* mouse micronucleus assays.

3.1.7 Carcinogenicity

There is no available information on the carcinogenicity of the dimethyltin compounds. Based on data from the mutagenicity studies of DMTC, the dimethyltin compounds are not expected to be genotoxic carcinogens. The histopathological effects from the repeat dose studies were reviewed.

This review indicated that the histopathological observations did not allow a prediction, either positive or negative, with respect to carcinogenicity.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

DMTC

Data from the DMTC repeated dose studies discussed above indicate no gross or histopathological effects on the reproductive tissues and organs (i.e., epididymis, ovary, seminal vesicle, testis, uterus, and vagina) of either sex. Histopathological evaluations were done on the reproductive tissues and organs in the two 90-day studies. In the dietary study, microscopic observations of the reproductive tissues and organs found no abnormalities in the mammary glands or testes, perivascular mononuclear cell infiltrate in the epididymides in 1/10 males in the 15 ppm dose group and 4/10 males in the control group, focal mineralization in the ovaries of 6/10 females (15 ppm) and 2/10 females (control), ovarian cysts in 1/10 females (15 ppm) and 3/10 females (control), and luminal dilatation in the uterus of 2/10 females at 15 ppm, 1/1 females at 6 ppm, and 1/10 females in the control group. None of these changes were statistically significant. No treatment-related changes or pathological findings were observed in the ovaries, epididymis, testes, uterus, vagina, or seminal vesicles of DMTC-exposed rats in the drinking water study.

The repeated-dose studies support the conclusion that DMTC at dietary doses up to 200 ppm (~17 mg/kg/day) produced no anomalies of the reproductive organs either grossly or microscopically. This dose did have effects on other organs. Therefore, the reproductive organs are not toxicological targets for DMTC and from these findings it is inferred that DMTC would not affect the physiological process of fertilization at 200 ppm.

DMTC is a neurotoxic substance and it is not known if DMTC can perturb the behavioral component of fertilization.

EHTG

To address the thioglycolate ligand hydrolysis product (EHTG), data from an OECD TG 421 study are available. Groups of male and female rats were exposed to doses of EHTG of 0, 10, 50 and 150 mg/kg bw/day by gavage. Parental systemic toxicity was observed in the 150 mg/kg/day group. It was characterized by: mortality, moribundity, decreased mean body weight gain, decreased consumption of feed, increased liver and kidney weight, or hepatocellular vacuolization in at least one sex of the F0 animals; and increased mucification of the cervical and vaginal epithelium in post-partum F0 dams. There were no test article-related effects on male and female mating and fertility indices, male copulation index or female conception index. Two females in the 150 mg/kg/day group were found dead on gestation day 21, near the time of expected parturition, 1 female was euthanized in extremis on gestation day 22 with signs of dystocia, and 1 female was euthanized due to total litter loss on lactation day 1. Within the limits of the experimental design, a dosage level of 50 mg/kg/day was considered to be the NOAEL for reproductive effects, fetotoxicity and systemic (maternal) toxicity resulting from exposure to EHTG when administered orally by gavage to rats (WIL Research 2005 cited in Epona Associates, LLC 2006a).

Conclusion

DMTC administered in drinking water or via the diet did not affect fertility in rats. Within the limits of the experimental design, a dosage level of 200 ppm (~17 mg/kg/day) was considered to be the NOAEL for fertility effects. For the thioglycolate ester EHTG, the NOAEL for reproductive effects, fetotoxicity and systemic (maternal) toxicity was established at 50 mg/kg/day.

Developmental Toxicity

DMTC

Data from full and partial gestational exposures to DMTC are summarized in Table 17.

Table 17 Summary of the Reproductive/Developmental Toxicity of DMTC

Method	Dose level	Exposure period	Results and Observations	Reference
Similar to OECD 414 (oral gavage)	5 mg/kg/day	Day 7-17	No treatment-related effects observed.	Noda 2001
	10 mg/kg/day		(NOAEL) No treatment-related effects observed.	
	15 mg/kg/day		(LOAEL) Treatment-related effects reported: • Reduced maternal body weight gain during days 10-220 of gestation ($p < 0.05$) • Clinical signs of toxicity, including piloerection, ataxia, perinasal and periocular staining, vaginal bleeding, tremor, and convulsion. • Significant reduction in fetal body weights (males and females) ($p < 0.05$).	
	20 mg/kg/day		Treatment-related effects reported: • Maternal death (2 animals, 1 each on days 18 and 19 of gestation). • Clinical signs of toxicity, including piloerection, ataxia, perinasal and periocular staining, vaginal bleeding, tremors, and convulsions. • Reduced maternal body weight gain during days 10-20 of gestation ($p < 0.01$). • Reduced maternal food intake ($p < 0.05$ or < 0.01). • Reduced maternal thymus weight ($p < 0.01$). • Increased incidence of post implantations loss (19.4% vs. 4.7% (not statistically significant) • Increased incidence of total resorptions (1 dam, not statistically significant) • Significant reduction in fetal body weights (males and females) ($p < 0.01$). • Increased incidence of fetuses with external malformations (22.5%), predominantly cleft palate ($p < 0.01$). • Increased incidence of fetuses with dilation of the renal pelvis ($p < 0.05$).	
Similar to OECD 414 (oral gavage)	20 mg/kg/day	Days 7-9, 10-12, 13-15, or 16-17	(LOAEL) Treatment-related effects reported (GD 10-12): • Significant ($p < 0.05$) reduction in maternal thymus weight and adjusted body weight gain in dams administered the test substance on days 10-12 of gestation.	Noda 2001

Method	Dose level	Exposure period	Results and Observations	Reference
	40 mg/kg day		Treatment-related effects reported: • Significant ($p < 0.05$ or $p < 0.01$) reduction in maternal thymus weight and adjusted body weight gain in dams of all treatment groups. • Significant ($p < 0.05$) increase in the incidence of fetuses with kinked ureters from dams administered the test substance on GD 16-17. • Significant ($p < 0.05$) increase in the incidence of visceral variations, i.e., splitting of the 1st cervical vertebral arches in fetuses from dams exposed on GD 7-9. • Significant ($p < 0.05$) increase in the incidence of skeletal variations, i.e., cervical ribs in fetuses from dams exposed on GD 7-9 or GD 13-15. • Total resorption in 1/10 dams (GD 7-9). • Reduced fetal body weight of females (GD 7-9)	

EHTG

To address the thioglycolate ligand hydrolysis product (EHTG), data from an OECD TG 421 study are available. Groups of male and female rats were exposed to doses of EHTG of 0, 10, 50 and 150 mg/kg-bw/day by gavage. Parental systemic toxicity was observed in the 150 mg/kg-bw/day group. Decreased viability and growth of the F1 animals through post-partum day 4 also occurred at the 150 mg/kg-bw/day dose. Within the limits of the experimental design, a dosage level of 50 mg/kg-bw/day was considered to be the NOAEL for reproduction effects, fetotoxicity and systemic (maternal) toxicity resulting from exposure to EHTG when administered orally by gavage to rats (BIBRA 1998 cited in Epona Associates, LLC 2006a).

Conclusion

DMTC was a developmental toxicant to rats in full and partial gestational exposures. DMTC induced fetotoxicity in the presence of severe maternal toxicity. Within the limits of the experimental design, a dosage level of 10 mg/kg/day was considered to be the NOAEL for developmental effects. There are no reproductive/developmental toxicity data specific for DMT(EHTG) or DMT(IOTG); however, data for DMTC are representative of the dimethyltin compounds for this endpoint (Refer to Section 1.4 for category justification).

For EHTG, a NOAEL of 50 mg/kg/day was established for reproduction effects, fetotoxicity and maternal toxicity. This result indicates that EHTG is less toxic than DMTC for the two hydrolysis products, DMTC and EHTG. Using data for DMTC to regulate DMT(EHTG) is health-protective for the reproductive/developmental endpoint There are no reproductive/developmental toxicity data specific for IOTG; however, data for EHTG are representative of IOTG for this endpoint.

4 HAZARDS TO THE ENVIRONMENT

DMT(EHTG) and DMT(IOTG) are isomers and are considered toxicologically equivalent; therefore, data for these materials are used interchangeably.

4.1 Aquatic Effects

DMTC, DMT(EHTG), and DMT(IOTG) have been tested for toxicity in a number of aquatic species. Study results considered reliable are summarized in Table 18.

Table 18 Summary of Effects of Dimethyltin Compounds and the Thioglycolate Esters on Aquatic Organisms

Organism	Method	Test System	Dura-tion	Test Substance	Result	Rating	Reference
DMTC							
Brachydanio rerio (freshwater fish)	OECD 203	Semi-static, measured	96 h	DMTC (99.66%): MMTC (0.25%): TMTC (0.09%)	LC50 > 100 mg /L NOEC ≥ 100 mg /L	2	Hooftman and de Wolf 2003a[1]
Pimephales promelas (freshwater fish)	OECD 203	Static, nominal	96 h	DMTC: MMTC (50:50%)	LC50 = 320 mg/L NOEC = 100 mg/L	2	Ward et al. 1996a
Cyprinodon variegates (marine fish)	OECD 203	Static, nominal	96 h	DMTC:MMTC (100% active ingredients)	LC50 > 1000 mg/L NOEC = 1000 mg/L	2	Boeri et al. 1995
Daphnia magna (freshwater invertebrate)	OECD 202	Static, measured	48 h	DMTC (99.66%): MMTC (0.25%): TMTC (0.09%)	EC50= 17 (12–24) mg/L NOEC = 3.2 mg/L	2	Hooftman and de Wolf 2003b[1]
Mysidopsis bahia (freshwater invertebrate)	OECD 203	Static, nominal	96 h	DMTC:MMTC (75:25%)	LC50 = 170 mg/L NOEC = 0.1 mg/L	2	Ward et al. 1996b
Scenedesmus subspicatus (freshwater algae)	OECD 201	Open, measured	72 h	DMTC (99.66%): MMTC (0.25%): TMTC (0.09%)	EC50 = 37 mg/L NOEC =1.1 mg/L	2	Oldersma et al. 2003[1]
Scenedesmus obliquus (freshwater algae)	Rand and Petrocelli c 1984	Unknown, nominal	96 h	Not reported	EC50 = 1.2 mg/L	2	Huang et al. 1993
Skeletonema costatum *(marine algae)*	OECD 201	Closed, nominal	72 h	DMTC (99% purity)	EC50 > 9.8 mg/L NOEC (growth) = 4.9 mg/L NOEC (cell density) = 0.98 mg/L	2	TR Wilbury 1996

Organism	Method	Test System	Dura-tion	Test Substance	Result	Rating	Reference
Skeletonema costatum *(marine diatom)*	OECD 201	Closed, nominal	72 h	DMTC:MMTC (75:25%)	LC50 (growth) > 100% WAF prepared at a loading rate of 100 mg/L LC50 (cell density) = 70 mg/L NOEC (growth) = 10 mg/L NOEC (cell density) = 10 mg/L	2	Ward et al. 1995a
Skeletonema costatum (marine diatom)	OECD 201	Closed, nominal	96 h	DMTC:MMTC (75:25%)	LC50 (growth) > 100% WAF prepared at a loading rate of 100 mg/L LC50 (cell density) = 310 mg/L NOEC (growth) = 10 mg/L NOEC (cell density) = 1.0 mg/L	2	Ward et al. 1995a
Skeletonema costatum (marine diatom)	Algal Growth	Open, analytical monitoring not reported	72 h	Not reported	EC50 > 0.93 mg/L	2	Walsh et al. 1985
Thalassiosira pseudonana (marine diatom)	Algal Growth	Open, analytical monitoring not reported	72 h	Not reported	EC50 > 0.93 mg/L	2	Walsh et al. 1985
DMT(EHTG)							
Pimephales promelas (freshwater fish)	OECD 203/ TSCA 797.1400	Static, nominal	96 h	DMT(EHTG) :MMT(EHTG) (75:25%)	LC50 > 100% WAF prepared at a loading rate of 100 mg/L NOEC (mortality/condition) = 100 mg/L	2	Ward et al. 1995b[1]

Organism	Method	Test System	Dura-tion	Test Substance	Result	Rating	Reference
Daphnia magna (freshwater invertebrate)	OECD 202/ TSCA 797.13 00	Static, nominal	48 h	DMT(EHTG) :MMT(EHTG) (75:25%)	EC50 = 32 (10–100) mg/L NOEC (mortality) = 10 mg/L	2	Ward et al. 1995c[1]
Daphnia magna (freshwater invertebrate)	OECD 211	Semi-Static, measured	21 d	DMT(EHTG): MMT(EHTG): Tin tetra(EHTG): TMT(EHTG) (89.01:9.92:0. 45:0.62 wt %)	LOEC = 2.3 mg/L NOEC = 0.46 mg /L	2	de Roode and de Haan 2004
Organism	**Metho d**	**Test System**	**Dura-tion**	**Test Substance**	**Result**	**Rating**	**Reference**
Pseudokirchneri ella subcapitata (freshwater algae)	OECD 201/ TSCA 797.10 50	Open, nominal	72 h	DMT(EHTG) :MMT(EHTG) (75:25%)	EC50 (growth) = 270 mg/L EC50 (density) = 120 mg/L NOEC (growth/densit y) = 10 mg/L	2	Ward et al. 1995d[1]
EHTG							
Daphnia magna (freshwater invertebrate)	DIN 38412, Test 11	Static, measured	48 h	99.5% purity	EC50 = 0.38 mg/L	2	Epona Associates, LLC. 2006a
Pseudokirchneri ella subcapitata (freshwater algae)	OECD 201	Open, measured	72 h	99.65% purity	EC50 (growth) = 0.91 mg/L EC50 (biomass) = 0.41 mg/L NOEC (growth/bioma ss) < 0.50 mg/L	1	Epona Associates, LLC. 2006a
IOTG							
Pimephales promelas (freshwater fish)	Similar to OECD 203	Static, nominal	96 h	> 98% purity	LC50 = 4.4 (3.9-4.9) mg/L NOEC < 3.2 mg/L	1	Epona Associates, LLC. 2006b
Daphnia magna (freshwater invertebrate)	OECD 202	Static, measured	48 h	99.05% purity	EC50 = 0.39 (0.28-0.53) mg/L	1	Epona Associates, LLC. 2006b

Organism	Method	Test System	Dura-tion	Test Substance	Result	Rating	Reference
Daphnia magna (freshwater invertebrate)	Similar to OECD 202	Static, nominal	48 h	> 98% purity	EC50 = 2.4 (1.9-3.3) mg/L	2	Epona Associates, LLC. 2006b

1Key study for this endpoint

TMTC = Trimethyltin chloride

Acute Toxicity Test Results

DMTC

The key fish, daphnia, and algae studies were performed using guideline methods and measured concentrations of dimethyltin. A mixture of DMTC:MMTC:TMTC (99.66:0.25:0.09%) was not acutely toxic to zebra fish (B. rerio) (96-h LC50 > 100 mg/L, NOEC ≥ 100 mg/L), and the 48-h EC50 and NOEC, with respect to daphnia mobility and condition, were 17 (12–24) mg/L and 3.2 mg/L, respectively. This same DMTC mixture produced an inhibitory effect on S. subspicatus growth at concentrations greater than 1.1 mg/L; the 72-h EC50 is 37 mg/L and the NOEC is 1.1 mg/L.

DMT(EHTG)/(IOTG)

The key fish, daphnia, and algae studies of a DMT(EHTG):MMT(EHTG) (75:25%) mixture were conducted following OECD Guidelines, using the Water Accommodated Fraction (WAF) method. The DMT(EHTG):MMT(EHTG) mixture was not acutely toxic to fathead minnows (*P. promelas*) (96-h LC50 > 100% WAF prepared at a loading rate of 100 mg/L), and the 96-h NOEC, based on nominal concentrations, was 100 mg/L. Based on nominal concentrations of a 75:25% mixture, the 48-h NOEC for *Daphnia magna* was 10 mg/L, and the 48-h EC50 was 32 (10–100) mg/L, and the. 72-h EC50 for *P. subcapitata* on growth and cell density values are 270 mg/L and 120 mg/L, respectively.

Chronic Toxicity Test Results

In a 21-day Daphnia magna reproduction study [OECD TG 211] conducted using a DMT(EHTG) mixture (Table 17), parental mortality was 100% at 50% and 100% of the Water-Accommodated Fraction (WAF) of DMT(EHTG). Reproduction of mobile offspring was not inhibited between 1 and 10% WAF, but could not be assessed at 50 or 100% WAF due to total parental mortality. The 21-day LC50 for parental survival was 1.03 mg/L; however, a clear dose-response relationship was not observed. The overall NOEC and LOEC were 0.457 mg/L (10% WAF) and 2.316 mg/L (50% WAF), respectively, based on measured concentrations of tin (used to estimate test substance concentrations) (de Roode and de Haan 2004).

Toxicity to Microorganisms

EC50 values for Micotox® assays using *Photobacterium phosphoreum* were 2.6 mg/L for DMTC (Dooley and Kenis 1987), and 0.1 mg/L for a filtered, saturated solution of DMT(IOTG) (Steinhaeuser et al. 1985). The 48-h IC50 values for DMTC are 3-11 mg /L for yeasts (Cooney et al. 1989).

4.2 Terrestrial Effects

Two acute toxicity studies of DMTC:MMTC mixtures with earthworms (*Eisenia fetida*) [OECD TG 207] were conducted in artificial soil. A 50:50 DMTC:MMTC mixture resulted in complete mortality at Day 14 at a nominal concentration of 1000 mg/kg. No mortality was observed at nominal concentrations of 0.10, 1.0, 10 and 100 mg/kg, and average weights were not significantly different from the control group. The 14-d LC50 was 140 (45-450 mg/kg) and the NOEC was 45 mg/kg, when calculated on an active ingredient basis. On a whole test substance basis, the 14-d LC50 was 320 (100-1000 mg/kg) and the NOEC was 100 mg/kg (Ward et al. 1995e).

The second study was conducted with a 75:25 DMTC:MMTC mixture. One earthworm died on Day 7 at a nominal concentration of 10 mg/kg; no deaths were reported at nominal concentrations of 0.1, 1.0, 100 or 1000 mg/kg. Relative to the control group, average weights were reduced 7 to 38% at all exposure levels. The 14-d LC50 was > 1000 mg/kg, and the NOEC (based on survival) was reported as 1000 mg/kg (Ward et al. 1996c)..

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7 ANNEX

As noted in Section 1.4, DMT(EHTG)/(IOTG) hydrolyze in acid and also in water to produce DMTC and the corresponding thioglycolate esters (EHTG/IOTG), which are covered under a separate HPV program managed by the Thioesters Association. The integration of the data for the organotins and corresponding ligands, EHTG and IOTG, is summarized in Table 19.

Table 19 Comparative Toxicology Data for the Dimethyltin Compounds, DMTC and DMT(EHTG)/(IOTG), and the Thioglycolate Esters, EHTG and IOTG

Endpoint	DMTC	DMT(EHTG)/ (IOTG)	EHTG	IOTG
Physico-chemical Data				
Melting point	90°C	-75 to -65°C	< -50°C	< -50°C
Boiling point	188-190°C @ 1013 hPa	≥290°C (decomp.)	119.5-171.1°C @ 9.5 hPa	117.5-161.8°C @ 9.5 hPa
Water solubility	823,000 mg/L	0.1-4.9 mg/L	4.7 mg/L	10.6 mg/L
Partition coefficient	-2.18	8.48	2.4	3.96
Vapour pressure	0.25 hPa @ 25°C	0.004 hPa @ 25°C	0.97 hPa @ 25°C	0.19 hPa @ 25°C
Density	1.4 g/cm^3	1.18 g/cm^3	0.97-0.98 g/cm^3	0.98 g/cm^3
Environmental Fate				
Photodegradation (Est. second order rate constants)	2.72 × 10E-12	27.7-29.1 × 10E-12	45.7 × 10E-12	45.0 × 10E-12
Stability in water	DMT stable	DMT stable	Not stable	Not stable
Transport Between Environmental Compartments (partition percentages)	Air: < 1 Water: 51.6 Soil: 47.3 Sediment: < 0.1	Air: 0.1-0.3 Water: 1.9-3.8 Soil: 27.5-27.8 Sediment: 68.2-70.4	Air: 3.8 Water: 45.6 Soil: 49 Sediment: 1.6	Air: 1.8 Water: 29 Soil: 68.2 Sediment: < 1
Biodegradation	Not readily biodegradable	Not readily biodegradable	Not readily biodegradable	Not readily biodegradable
Ecotoxicity				
Acute fish (96-h LC50)	100 mg/L NOEC = 100 mg/L	> 100% WAF (prepared at a loading rate of 100 mg/L) NOEC = 100 mg/L	9 mg/L (48-h LC50)	4.4 (3.9-4.9) mg/L NOEC < 3.2 mg/L
Acute daphnia (48-h EC50)	17 (12-24)mg/L NOEC = 3.2 mg/L	32 (10-100) mg/L NOEC = 10 mg/L	0.38 mg/L	0.39 (0.28-0.53) mg/L
Chronic daphnia	No data	NOEC = 0.46 mg/L LOEC = 2.3 mg/L	No data	No data
Toxicity to algae (72-h EC50)	Growth = 37 mg/L Biomass = 11.8 mg/L NOEC = 1.1 mg/L	Growth = 270 mg/L Density = 120 mg/L NOEC = 10 mg/L	Growth = 0.91 mg/L Density = 0.41 mg/L NOEC = 0.50 mg/L	No data, see EHTG

Endpoint	DMTC	DMT(EHTG)/ (IOTG)	EHTG	IOTG
Mammalian Toxicity				
Acute inhalation (LC50)	115–125,000 mg/m^3	> 1968–132,000 mg/m^3	510 mg/m^3	43,000 mg/m^3
Acute dermal (LD50)	380 – > 2000 mg/kg bw	> 1050– > 3100 mg/kg bw	> 2000 mg/kg bw	> 2000 mg/kg bw
Acute oral (LD50)	74–564 mg/kg	1150–1710 mg/kg	303–1120 mg/kg bw	485 mg/kg bw
Irritation (skin)	Corrosive	Slight irritant	Slight irritant	Slight irritant
Irritation (eye)	Severe irritant	Slight irritant	Slight irritant	Slight irritant
Sensitization	No sensitization	Weak sensitizer	Weak sensitizer	Weak sensitizer
Repeated dose toxicity (NOAEL)	1 mg/kg/day (90 d oral)	See DMTC	168-1763 mg/kg/day (28 d oral)	3.2 ppm (14 d inhalation)
Reproduction/ developmental toxicity (NOAEL)	10 mg/kg/day	See DMTC	50 mg/kg/day	See EHTG
In vitro genetic toxicity (Ames)	Negative	Negative	Negative Ambiguous[1]	Negative
In vivo genetic toxicity	Negative	See DMTC	Negative	See EHTG

1 In vitro mammalian chromosome aberration test

Data for EHTG and IOTG were obtained from the IUCLID dossiers prepared by Epona Associates, LLC (2006a,b).