201-15606A

U.S. High Production Volume (HPV)
Chemical Challenge Program

Tin bis(2-ethylhexanoate) Test Plan

Prepared by

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

3 MARCH 2004

Introduction

Tin bis(2-ethylhexanoate) (Tin EHA) is the stannous salt of 2-ethylhexanoic acid (EHA). It readily dissociates to the corresponding metal cation (Sn^{++}) and 2-ethylhexanoate anions. Both the metal cation and the carboxylic acid have robust data bases of health and environmental data. In addition, 2-ethylhexanoic acid has already been reviewed in the OECD SIDS process.

HPV endpoints are fulfilled using a combination of data from the parent molecule, (Tin EHA) as well as for the dissociation products. Stannous chloride data have been provided to characterize the health and environmental effects of the tin (II) cation. The dossier for EHA is included to characterize the contribution of the carboxylic acid portion of the molecule. Selected testing of Tin EHA is proposed to further fulfill HPV endpoints. Robust summaries are provided for the relevant existing information for the tin EHA and its dissociation products. The proposed testing is presented in Table 2.

Sponsored Chemical Information

This compound is sponsored by the Metal Carboxylates Coalition (The Coalition) managed by the Synthetic Organic Chemical Manufacturers Association (SOCMA) Visions Department. The Coalition is pleased to submit a justification, Test Plan and Robust Summaries for the following compound sponsored under the U.S. High Production Volume (HPV) Challenge Program:

Chemical name	CAS#
Hexanoic Acid, 2-Ethyl,Tin (II) salt	301-10-0
Dissociation Products:	
Hexanoic Acid, 2-Ethyl	149-57-5
Tin (2+) Chloride	7772-99-8

Use Pattern

Metal carboxylates function to deliver a metal ion into chemical reactions. The carboxylic acids (acids) are tailored for use in different products or chemical reactions.

Tin 2-ethylhexanoate is used primarily as a crosslinking agent in the production of flexible polyurethane foams and as a catalyst in the production of polymers. In these uses free 2-ethyl hexanoic acid (2-EHA) is liberated and then can be trapped in the final polymer product as either a polymer end group (as the ester) or it can remain as the small free acid molecule. The tin atom is incorporated into the polymer product, most likely as the tin(II) alcoholate (Sn-OR). If hydrolysis occurs, tin oxides (SnO and SnO2) would be formed.

Dissociation Studies

Metal carboxylates readily dissociate in water. Dissociation is a reversible process and the portion of dissociated salt present is dependent on the pH and pKa (the dissociation constant), which is the pH at which 50% dissociation occurs. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for tin EHA. The transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH.

Dissociation studies have been conducted which indicate that significant dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while complete dissociation will occur at physiologically relevant pH of the mammalian stomach (pH 1.2). These findings are particularly important in relating available data for the respective acid and metal to support the existing data for the salts and in the fulfillment of critical endpoints. The dissociation studies presented here were conducted according to OECD Guideline 112.

The pKa and pH are equal when the parent compound (metal carboxylate salt) is 50% dissociated. Tin EHA is shown in Figure 2. This figure shows tin 2-ethylhexanoate. Ionic charges for each acid are –1 and the metal is +2.

The dissociation constant is important for two reasons. First, it determines the proportion of any specific acid or metal that is dissociated at a given pH. The free acid anion and corresponding free metal cation are often much different than the salt (ion pair) moiety in characteristics such as solubility, adsorption, and toxicity. The proportion of dissociation influences the behavior of the substance in the environment and bioavailablity of the acid and metal constituents of metal carboxylate salts.

The dissociation constant reported in Table 1 indicates tin EHA has a pKa value (pKa1) in the neutral range (5.088). This indicates that in the neutral pH range, significant portions of will be dissociated. In addition, at the low pH of the mammalian stomach (pH 1.2) all of the metal carboxylates would be expected to be completely or nearly completely dissociated. The pKa of the salt and the acid are very similar and should dissociate in a similar manner at both environmental and biologically relevant pH values. This indicates that the absorption and any observed toxicity would be dependent upon the sum of the toxicities for the respective acid and metal when administered orally.

Figure 1: Structure of 2-ethylhexanoic acid

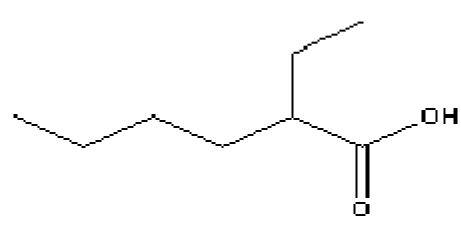
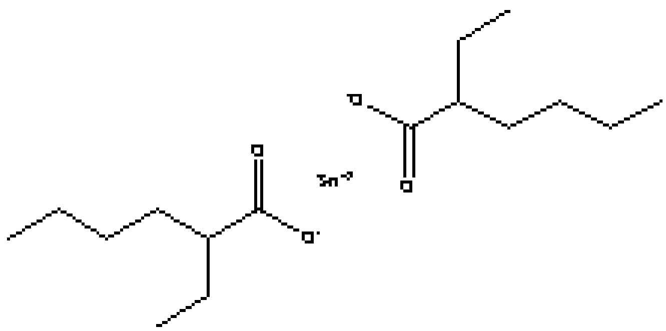


Table 1: Dissociation Constant

Chemical	CAS#	pKa Value (mean of 3)
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0	5.088 (measured)
Hexanoic Acid, 2-Ethyl	149-57-5	4.89 (from CRC Handbook of Chemistry and Physics)

Figure 2: The Structure of Tin 2-ethylhexanoate



The dissociation constants show that at the pH of the stomach and at the pH of environmental media the important moieties are the ionized free acid and metal. Because of this, environmental fate, ecotoxicity, and mammalian toxicity of the acid can to serve as a surrogate data for the acid component of respective metal salt. Similarly, under these conditions, data for the metal ion can be represented by fate and toxicity data of free metal ion or simple metal salts (e.g., metal chlorides). Therefore, the role in any observed toxicity for acids and metals can be evaluated independently (i.e., as the free metal and/or free acid) and one can determine the contribution of each portion of the molecule to the estimated effects.

The robust summaries for tin EHA are attached as Appendix I. This contains the data for the parent material and the estimated data for applicable endpoints when the data could be estimated from the dissociation products.

The robust summaries for 2-ethylhexanoic acid were made available to the Coalition by the American Chemistry Council Oxo Process Panel, the members of which volunteered to provide the information to the OECD SIDS program. The 2-ethylhexanoic acid data are attached as Appendix II.

The robust summaries for stannous chloride, a common, water soluble divalent tin salt, are attached as Appendix III.

Summary

In summary, the key points relative to the tin 2-ethylhexanoate evaluation are:

- The dissociation constant (pKa) is in the approximately neutral range (5.088);
  - Complete or nearly complete dissociation at gastric and cytosolic pH levels;
  - A moderate to high proportion of dissociation in the environmental pH range;
- Bioequivalency of salts to that of the metal cation and acid anion;
- Data are provided for the parent molecule and both of its dissociation products.

Proposed Test Plan

The existing data for the metal carboxylate salts have been summarized in robust summaries and ranked for reliability according to EPA Guidance. The Coalition has gathered existing data for the dissociation products, the respective metal and acid and prepared robust summaries for these as well.

Available data are summarized in Table 2. In addition to the data available for the salt there is a complete set of robust summaries for the acid, 2-ethylhexanoic acid, which has already been assessed in the OECD SIDS program. Summaries of available data for the metal are provided by using data for stannous chloride.

Environmental Fate Parameters:

Physical chemical properties information have been developed for the tin EHA. Based upon demonstrated dissociation of this salt and the refractory nature of the metal, biodegradation will depend primarily on the free acid. Since the acid (2- ethyl hexanoate) has reliable biodegradation data, the Coalition will rely upon data for the acid to characterize the degradability of tin EHA.

Ecotoxicity:

Reliable ecotoxicity data are available for the 2-ethylhexanoic acid, and some data are available for stannous chloride. Two ecotoxicity studies are proposed for the tin 2-ethylhexanoate salt. Acute fish and algal toxicity data will be developed for the tin EHA. There are data for daphnia for both dissociation products, and no daphnia data will be developed.

Human Health Effects:

A 7 day repeated dose toxicity study will be performed to demonstrate that the toxicity of the tin EHA is not more than the toxicity of the dissociation products. Since the molecule is essentially completely dissociated at stomach pH, the use of the data from the *in vivo* studies for genotoxicity, repeated dose toxicity and reproduction/developmental effects.

Table 2

Summary of Available Data for tin EHA and its dissociation products

Physical/Chemical Properties	**Tin 2-Ethylhexanoate**	**2-Ethylhexanoic Acid (2-EHA)**	**Stannous Chloride**
CAS#	301-10-0	149-57-5	7772-99-8
Molecular weight	405.1	144.2	189.6
Melting Point	< 45 C	37.72 (MPBPWIN)	~247 C
Boiling Point	453 C (est MPBPWIN)	234.2 (MPBPWIN)	623 – 652 C
Vapor Pressure	1.25 E-8 (est MPBPWIN)	.0626 (MPBPWIN)	
Partition Coefficient (log Pow)	2.67	~ 3 (calculated)	Not applicable
Water Solubility	~ 100 mg/l	25 mg/L at 25°C	> 10,000 mg/l
Photodegradation			
Stability in water	pKa 5.09 @ 20C (measured)	pKa = 4.89 (CRC Handbook)	
Biodegradation	Anticipated to be biodegradable based on data for 2-EHA, and low toxicity of Sn^{+2} to fish and daphnia	BOD20 = 83% of ThOD	Not applicable for inorganic salt
Environ. Transport % EPIWIN Level III Fugacity Model	Air 4.14 Water 29.5 Soil 66.2 Sediment 0.16	Air 5.29 Water 41.6 Soil 53 Sediment 0.2	

Environmental Parameters	**Tin 2-Ethylhexanoate**	**2-Ethylhexanoic Acid (2-EHA)**	**Stannous Chloride**
Acute Fish: 96 hr LC50	To be tested	70 mg/L after 96 hours at a pH of 5.3-5.5	>0.035 mg/l as Sn (only saltwater species tested)
Acute Daphnid 48 hr EC50	> 30 mg/l estimated based on data for 2-EHA and Sn^{+2}	85.38 mg/L (slightly toxic),	19 – 55 mg/l as Sn
Algae 72 hr EC50	To be tested	96 hr EbC_{50} = 40.616 mg/L 96 hr EuC_{50} = 44.390 mg/L	0.325 mg/l as Sn

Health Effects	**Tin 2-Ethylhexanoate**	**2-Ethylhexanoic Acid (2-EHA)**	**Stannous Chloride**
Rat acute oral LD50	3400 - 5870 mg/kg (measured)	1600 - 3200 mg/kg	720 - 1745 mg/kg
Irritation	slightly irritating to skin (measured)	Slight necrosis – corrosive	Corrosive to skin
Repeat dose	To be tested - 7 day repeat dose study to bridge to 2-EHA	90 day oral: Rat dietary, NOAEL = 5000 ppm in the diet (~ 300 mg/kg/day). NOEL = 1000 ppm in the diet (approximately 65 mg/kg/day). All toxicity was reversible within 28 days.	NOEL, 90 day, rats and mice : 1900 ppm in diet
Genotoxicity (*In Vitro*) Bacterial - Ames Test	Not mutagenic (measured)	Not mutagenic	Not mutagenic
Genotoxicity (*In Vitro*) Mammalian Cells			Weight of evidence not a clastogen
Genotoxicity *in vivo*	not clastogenic – estimated based on data for dissociation products	Not clastogenic - mouse micronucleus test	Not clastogenic in rats or mice
Reproductive		Equivocal reproductive findings were observed in male rats at 600 mg/kg/day. Rat, 1 –generation reproduction test; NOEL for P generation: 300 mg/kg NOEL for F1 generation: 100 mg/kg	
Developmental toxicity	NOEL > 100 mg/kg estimated based on data for dissociation products	Several studies have demonstrated that high oral doses of 2-EHA can cause developmental toxicity in rats and mice, but not in rabbits. Rat, oral, NOEL for maternal animals = 300 mg/kg/day NOEL for offspring = 100 mg/kg/day	Not teratogenic when tested in rats and mice up to 50 mg/kg
Other data	80 week study in rats, 1% in diet weeks 0-8; 0.5 % in diet during weeks 12 – 80; not carcinogenic		Not carcinogenic; rat, mice exposed to 1000 and 2000 ppm in diet

SUMMARY

The Test Plan reflects the combined use of salt and dissociation product data to address the HPV data elements. Proposed testing is focused on determination of environmental effects in fish and algae and also an oral study to confirm that the oral toxicity of the salt is similar to that of the dissociation products.