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

FINAL SUBMISSION

Zinc (2-ethylhexanoate)

Prepared by

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

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INTRODUCTION

Zinc 2-ethylhexanoate is the zinc metal salt of 2-ethylhexanoic acid (EHA). It readily dissociates to the corresponding metal cation, Zn^{++} and 2-ethylhexanoate anions. The carboxylic acid (EHA) has a robust data base of health and environmental data and has already been reviewed in the OECD SIDS process. The metal cation and the organic anion are considered to represent the overall toxicity of the zinc 2-ethylhexanoate (Zn EHA) in a manner proportionate to the parent acid and metal. The EPA guidance document High Production Volume Challenge Program "Development of Chemical Categories in the HPV Challenge Program", allows for the use of the acid data as a surrogate for the salts if the degree of dissociation is similar in the media of concern and the counter ion does not contribute any more (or less) toxicity.

HPV endpoints are fulfilled using a combination of data from the parent molecules and the dissociation products. The dossier for EHA is included to characterize the contribution of the carboxylic acid portion of the molecule. Robust summaries are provided for the relevant existing information for the parent molecule and the dissociation product. The data are presented in the attached Test Plan matrix (Table 2). The *in vivo* mammalian toxicity profile will be dominated by the acid moiety. The environmental profile will be driven by zinc but will be modulated by water solubility and degree of dissociation.

METAL CARBOXYLATES CATEGORY

Sponsored Chemical Information

Hexanoic Acid, 2-Ethyl, Zinc Salt (Zn EHA; CAS Number 136-53-8) is sponsored by the Metal Carboxylates Coalition (The Coalition) managed by the Synthetic Organic Chemical Manufacturers Association (SOCMA) Association Management Center.

Use Patterns for Metal Carboxylates

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

Zn EHA is used as a catalyst for polyurethane systems (foams) and for unsaturated polyester resin systems (boats, shower stalls, etc.). It is also used in liquid stabilizer formulations that allow flexible PVC to be processed.

Dissociation Studies

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. 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. Accordingly, the dissociation constant is important because it determines the proportion of any specific acid or metal that is dissociated at a given pH.

The proportion of dissociation, then, directly influences the behavior of the substance in the environment and bioavailability of the acid and metal constituents of metal carboxylate salts. 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.

Metal carboxylates readily dissociate in water. 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 structure for Zn EHA is shown in Figure 1 and Table 1 shows that the pKa values, 4.89 and 6.99, respectively, for hexanoic acid and its zinc salt. The dissociation studies presented here were conducted according to OECD Guideline 112. These values, then, predict high water solubility for the salts at environmental and physiological pH and suggest that salts will distribute similarly in the environment and have similar residence times in environmental compartments. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for Zn EHA. 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. The *in vivo* toxicity profile will be dominated by the acid moiety and the environmental profile will be affected by the water solubility and degree of dissociation.

More specifically, according to a standard reference text,

> "Zinc is important as an essential trace element in all living systems from bacterial to humans. The toxicity of zinc and most zinc-containing compounds is generally low and, with certain exceptions, of minor importance compared with the significance of zinc deficiency in plants, animals and man."
>
> Ohnesorge, F. K. and Michale Wilhelm, pp1309, Metals and their Compounds in the Environment. Ernst Merian, ed. VCH Publishers, Weinheim, Germany 1991.

Figure 1: **Hexanoic acid, 2-ethyl-, zinc salt**
RN: 136-53-8

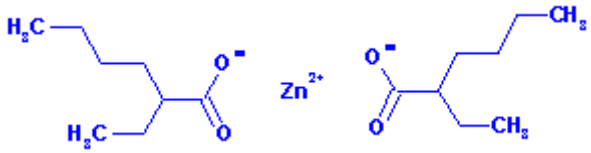

Table 1: Dissociation Constants

Chemical	CAS#	pKa Value (mean of 3)
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8	6.99 (Wildlife Int., 2002)
Hexanoic Acid, 2-Ethyl	149-57-5	4.89 (from CRC Handbook of Chemistry and Physics)

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 serve as surrogate data for the acid component of the 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 EHA are in Appendix I, and those for Zn EHA are in Appendix II. The robust summaries for zinc chloride are in Appendix III. These contain 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 EHA 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.

Summary

In summary, the key points relative to the Zn EHA evaluation are:

- The dissociation constants (pKa) are in the approximately neutral range;
  - 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 is assumed.

Proposed Test Plan

The existing data for Zn EHA and its dissociation products have been summarized in robust summaries and ranked for reliability according to EPA Guidance. Available data are summarized in Table 2. In addition to the data available for Zn EHA there is a complete set of robust summaries for EHA, which has already been assessed in the OECD SIDS program and for zinc chloride.

Physical Chemical Properties

Physical chemical properties information is available for Zn EHA (Table 2). Additional physical chemical data for EHA and zinc chloride are also provided in Table2.

Environmental Fate Parameters:

Environmental fate data have been modeled for Zn EHA using Epiwin (Table 2). Biodegradation will depend primarily on the free acid. EHA is biodegradable; similar results are expected for Zn EHA. 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 of the acid can to serve as surrogate data for the acid component of the respective metal salt. Similarly, under these conditions, data for the metal ion can be represented by fate data of free metal ion or simple metal salts (e.g., metal chlorides). Therefore, the role in the environmental fate 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.

Ecotoxicity:

An acute toxicity to daphnia study is available for Zn EHA. Reliable ecotoxicity data (fish, daphnia and algae) are also available for zinc chloride and EHA. Since Zn EHA dissociates at environmental pH, the data for the dissociation products can be used to represent the aquatic toxicity of Zn EHA (Table 2).

Human Health Effects:

A 7-day repeat dose oral study in rats with Zn EHA is available (Table 2). Since the Zn EHA is essentially completely dissociated at stomach pH, the use of the data from the health effects studies for the dissociation products (EHA and zinc chloride) can also be used to represent the toxicity of Zn EHA.

Table 2. Available and Estimated Data for 2-ethylhexanoic acid, Zn EHA and zinc chloride

Chemical	**EHA**	**Zn EHA**	**Zinc Chloride**
Physical/Chemical Properties			
CAS#	149-57-5	136-53-8	7646-85-7
Molecular weight	144.2	353.4	136.3
Melting Point	37.72 (MPBPWIN)	-47 ºC	290ºC
Boiling Point	234.2 (MPBPWIN)	Could not be determined (> 400 ºC)	732ºC
Vapor Pressure mm Hg	0.0626 (MPBPWIN)	1.59E-006 mm Hg (MPBPWIN)	1 mm Hg @ 428ºC

Partition Coefficient (log Pow)	~ 3 (calculated)	~3 estimated	Not applicable
Water Solubility	25 mg/L at 25°C	20.2 mg/L @ 25°C	$4.32X10^6$ mg/L @25ºC
Environmental Fate			
Photodegradation	Not available	OVERALL OH Rate Constant = 12.7363 E-12 cm3/molecule-sec HALF-LIFE = 10.078 Hrs	Not applicable
Stability in water	pKa 4.89	pKa = 6.99 @ 20 C	
Biodegradation	BOD_{20} = 83% of ThOD	Anticipated to be biodegradable based on data for EHA	Not applicable
Environ. Transport % EPIWIN Level III Fugacity Model	Air 5.29 Water 41.6 Soil 53 Sediment 0.2	Air 1.26 Water 31 Soil 62.3 Sediment 5.49	Not applicable
Environmental Effects			
Acute Fish: 96 hr LC50	LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5	LC_{50} ~ 9 -1000 µg salt/L (estimated) based on data for $ZnCl_2$.	96 hr LC_{50} = 93-0.815µgZn/L (trout)
Acute Daphnid 48 hr EC50	48 hr EC_{50} = 85.38 mg/L	48 hr EC50 = 14 mg/L; EC50 ~ 8650µg salt/L (estimated) based on data for $ZnCl_2$.	48 hr EC_{50} = 799 µg Zn/L
Algae 72 hr EC50	96 hr EbC_{50} = 40.616 mg/L 96 hr EuC_{50} = 44.390 mg/L	EC50 ~ 480µg salt/L (estimated) based on data for $ZnCl_2$.	96 hr EC_{50} = 44.7 µg Zn/L
Health Effects			
Rat Acute Oral LD50	LD_{50} = 1600 - 3200 mg/kg	LD_{50} = 3550 – 3700 mg/kg	LD_{50} = 528 mg/kg As Zn; 1000mg/kg as $ZnCl_2$
Rabbit Acute Dermal LD_{50}	LD_{50} = 6.5ml/kg	LD_{50} = >5g/kg	No data
Rat Acute Inhalation LC_{50}	LC_{50} > 2.36 mg/l	LC_{50} = >23.3mg/l	No data
Repeat Dose oral	90-day rat/diet NOAEL = 0.5% (ca. 300	7-day rat/gavage NOEL = 1000 mg/kg bw/d	90-day NOAEL rat/diet = 3000 ppm (ca. 240 mg

	mg/kg/day); NOEL = 0.1% (ca. 65 mg/kg/day		$ZnCl_2$/kg/day); 90-day NOAEL mouse/diet = 3000 ppm (ca. 465 mg $ZnCl_2$/Kg /day)
Genotoxicity (*In Vitro*) Bacterial - Ames Test	Not mutagenic	Not mutagenic	Negative for reversion, prophage induction and comutagenesis in E. coli cells. Exogenous metabolic activation not employed
Genotoxicity (*In Vitro*) Mammalian	Not clastogenic, based on in vivo testing of 2-ethylhexanol (2-EHOH). The data from 2-ethylhexanol is directly applicable to the assessment of this endpoint for 2-ethylhexanoic acid due to the extensive metabolism of the former to the latter in vivo.	No data	Negative for mutation in cultured L5178Y mouse lymphoma cells. Exogenous metabolic activation not employed.
Genotoxicity in vivo	Not clastogenic - mouse micronucleus test	No data	In vivo chromosome aberration studies in male C57B1 mice exposed orally (diet) for one month. A statistically-significant increase in structural aberrations as reported for animals receiving a low calcium diet and zinc; aberrations were also increased but not statistically in mine receiving a normal calcium diet.

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	No data	A one-generation breeding study with Sprague-Dawley rats used oral gavage of 7.5, 15 or 30 mg $ZnCl_2$/kg/day for 77 days prior to mating and through weaning. In a separate study, no histological alterations in testes or ovaries were reported in mice receiving 1110mg Zn/kg/day orally for 13 weeks.
Developmental toxicity	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 = 250-300 mg/kg/day depending on route of administration NOEL for offspring = 100 mg/kg/day	No data	Various zinc salts have been evaluated for the ability to produce terata and/or fetotoxicity in rodents. Oral and ip routes of administration have been employed. Guideline developmental toxicity protocols have generally not been followed in this testing. Oral administration of 100mg Zn/kg/day to rats for 21 days prior to pregnancy had no effect on fetal development. There are conflicting reports of development effect at zinc dose of 200-250 mg/kg/day during gestation, but it is likely that

			administration of zinc at levels above 200mg/kg/day can produce developmental toxicity in rodents.

SUMMARY

The Test Plan reflects the combined use of Zn EHA, zinc chloride and EHA data to address the HPV data elements for Zinc EHA. All HPV endpoints have been fulfilled.

APPENDIX I
ROBUST SUMMARIES: 2-ETHYLHEXANOIC ACID

APPENDIX II
ROBUST SUMMARIES: ZINC ETHYLHEXANOATE

APPENDIX III
ROBUST SUMMARIES: ZINC CHLORIDE