201-14172

[illegible] "Hobson" <hobsonjfxxxxxx@msn.com> on 12/26/2002 10:29:45 AM

To: oppt.ncic@epamail.epa.gov, Rtk Chem/DC/USEPA/US@EPA
cc:

Subject: Metal Carboxylates Category Justification Document. Test Plan and Robust Summaries

Attached please find a cover letter for submission of the Category Justification and Development Document, Test Plan and Robust Summaries for the Metal Carboxylates Category.

The documents were created in WORD and have been stored as WORD 97/RTF

Please send a receipt confirming delivery via email

Please contact me if you have questions about this email

James F. Hobson, Ph.D., DABT

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CategoryJustification & Test Plan Document Metal Carboxylates.zip

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SOCMA

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SYNTHETIC ORGANIC CHEMICAL MANUFACTURERS ASSOCIATION

201-14172

2002 DEC 27 PM 12: 35

December 23, 2002

RETURN RECEIPT REQUESTED, PLEASE, BY E-MAIL

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

ATTN: Chemical Right-To-Know Program

RE: Test plan submission pursuant to the High Production Volume Challenge for a category of Metal Carboxylates

Dear Administrator Whitman:

The Metal Carboxylates Coalition organized under the Synthetic Organic Chemical Manufacturers Association (SOCMA) is pleased to submit a test plan and robust summaries for the following compounds sponsored under the U.S. High Production Volume (HPV) Challenge Program:

Sponsored Chemical	*CAS#*
Cobalt Acetate	71-48-7
Propionic Acid, Calcium Salt	4075-81-4
Propionic Acid, Cobalt (2+) Salt	1560-69-6
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0
Naphthenic Acids, Cobalt Salt	61789-51-3
Naphthenic Acids, Zinc Salt	12001-85-3
Neodecanoic Acid, Cobalt Salt	27253-31-2
Aluminum Distearate	300-92-5
Cobalt Stearate	13586-84-0
Barium Distearate	6865-35-6
Aluminum Tristrearate	637-12-7
Phenol, Nonyl, Barium Salt	28987-17-9
Fatty Acids, C9-13-Neo- Cobalt Salts	68955-83-9
Cobalt Borate Neodecanoate Complexes	68457-13-6
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4

Sponsoring companies who are members of this consortium are:

Akcros Chemicals Ltd.
Baerlocher USA
Crompton Corporation
CONDEA Servo
ATOFINA Chemicals, Inc.
Ferro Corporation
Kemin Industries, Inc.
OM Group, Inc.
Pelron Corporation
Rohm & Haas Company
The Shepherd Chemical Company
Troy Corporation

The Metal Carboxylates Coalition is a consortium managed by SOCMA's Association Management Center. The contact for the Metal Carboxylates Coalition is Lynne Jones. She can be reached by telephone at 202-721-4157, by fax at 202-296-8120 or by e-mail at jonesl@socma.com .

Sincerely,

Lynne Jones
Executive Director

Cc: Metal Carboxylates Coalition
B. Lesczynski – OPPT, EPA
R. Hefter – OPPT, EPA

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

CATEGORY DEVELOPMENT AND JUSTIFICATION, AND PROPOSED TEST PLAN FOR THE METAL CARBOXYLATES CATEGORY

Prepared by

MorningStar Consulting, Inc.

on behalf of

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

DECEMBER 20, 2002

TABLE OF CONTENTS

SUMMARY 6

METAL CARBOXYLATES CATEGORY 6

USE PATTERNS FOR METAL CARBOXYLATES 7

Common Characteristics of Metal Carboxylates 7

Dissociation Studies 8

SUBCATEGORIES 16

Rationale 16

PROPOSED TEST PLAN 16

PROPOSED TESTING BY SUBCATEGORY 18

Subcategory 1- Acetates and Propionates 18

Subcategory 2 - 2-Ethylhexanoate Salts 19

Subcategory 3 - Naphthenates 21

Subcategory 4 -: Neodecanoic and Fatty Acids 23

Subcategory 5 - Barium Nonyl Phenol 24

Subcategory 6 - Stearates and Fatty Acids, Tall-Oils 25

TABLE OF FIGURES

FIGURE #	TITLE	PAGE
FIGURE 1	Structures of Representative Carboxylic Acids Found in Metal Carboxylates	7
FIGURE 2	Structures of Representative Metal Carboxylate Salts	9
FIGURE 3:	Carboxylic Acids Found Subcategory 6	23

TEXT TABLES

TABLE #	TITLE	PAGE
Table 1:	Dissociation Constants for 20 Metal Carboxylates	10
Table 2:	Results of Extraction of Cobalt from Surrogate Biological Fluids	13
Table 3:	List of Subcategories	17
Table 4:	Subcategory 1: Acetates and Propionates	18
Table 5:	Subcategory 2 – 2-Ethylhexanoates	19
Table 6:	Subcategory 3 – Naphthenates	21
Table 7:	Subcategory 5 - Neodecanoic and Fatty Acids	23
Table 8:	Subcategory 5 - Barium Nonyl Phenol	24
Table 9:	Subcategory 6 - Stearates and Fatty Acids, Tall Oils	25

ATTACHED TABLES AND MATRICES

TABLE I **TEST PLAN MATRIX**

TABLE II **METALS DATA MATRIX**

TABLE III **ACIDS DATA MATRIX**

SUBCATEGORY MATRICES

Matrix 1	**Existing Data for Subcategory 1**
Matrix 2	**Existing Data for Subcategory 2**
Matrix 3	**Existing Data for Subcategory 3**
Matrix 4	**Existing Data for Subcategory 4**
Matrix 5	**Existing Data for Subcategory 5**
Matrix 6	**Existing Data for Subcategory 6**

SUMMARY

The Metal Carboxylates Category includes 20 compounds that are metal salts of carboxylic acids. These compounds readily dissociate to the corresponding metal and carboxylic acid. HPV endpoints are fulfilled using a combination of data from the parent molecule, as well as for the dissociation products; that is, a metal salt and/or a carboxylic acid. Selected testing of the parent molecules has been proposed to further fulfill HPV endpoints. Robust summaries are provided for the parent molecules. Supporting data for the dissociation products are included within the remarks section of the Robust Summaries. The proposed testing is presented in the attached Test Plan matrix (Table I)

METAL CARBOXYLATES CATEGORY

The Metal Carboxylates Category (Category) includes 20 compounds that are metal salts of carboxylic acids (see list below). The Category is sponsored by the Metal Carboxylates Coalition (The Coalition) a consortium managed by Synthetic Organic Chemical Manufacturers Association's (SOCMA) Association Management Center. The Coalition is pleased to submit a Category development and justification, Test Plan and Robust Summaries for the following compounds sponsored under the U.S. High Production Volume (HPV) Challenge Program:

Chemical name	CAS#
Cobalt Acetate	71-48-7
Propionic Acid, Calcium Salt	4075-81-4
Propionic Acid, Cobalt (2+) Salt	1560-69-6
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0
Naphthenic Acids, Cobalt Salt	61789-51-3
Naphthenic Acids, Zinc Salt	12001-85-3
Phenol, Nonyl, Barium Salt	28987-17-9
Neodecanoic Acid, Cobalt Salt	27253-31-2
Fatty Acids, C9-13-Neo- Cobalt Salts	68955-83-9
Cobalt Borate Neodecanoate Complexes	68457-13-6
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4
Aluminum Distearate	300-92-5
Cobalt Stearate	13586-84-0
Barium Distearate	6865-35-6
Aluminum Tristrearate	637-12-7

Each compound includes a carboxylic acid moiety with a range of alkyl chain lengths and one of nine different metals cations (aluminum, barium, boron, cobalt, calcium, potassium, tin, zinc or zirconium).

Use Patterns for Metal Carboxylates

The 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.

In general the cobalt carboxylates are used as oxidative polymerization catalysts in many product areas. These areas include but are not limited to: Ink and paint driers; unsaturated polyester resins, and hydrodesulfurization in the manufacturing, making of DEET (diethyltoluamide). Some of these carboxylate compounds are used in oxygen scavenger plastics as well (for example, plastic bottles). The tire industry also uses cobalt carboxylate compounds as adhesion promoters in part of the tirestire manufacturing. These compounds help with the adhesion between the rubber in the steel cords. The metal (not salt) loadings range from 0.01-0.5% depending upon the application.

Potassium 2-ethylhexanoate is used as a catalyst for polyurethane systems (foams) and for unsaturated polyester resin systems (boats, shower stalls, etc.). Zinc carboxylate compounds are used as catalysts in paints and coatings; and in polyurethanes. They are used as heat stabilizers for PVC and as a heat and/or friction modifiers for lubricants and greases. Zinc carboxylate compounds can also be used as wetting agent for pigments in organic systems.

Zirconium carboxylate compounds are used as catalysts in inks, paints and coatings.

Common Characteristics of Metal Carboxylates

The Metal Carboxylates Category consists of 20 metal carboxylates. The compounds encompass nine metals (primarily in the divalent form) associated with carboxylic acids with varying chain lengths, differences in saturation and differences in branching[1]. The nine metals represented in this category are aluminum (Al), barium (Ba), boron (B), cobalt (Co), calcium (Ca), potassium (K), tin (Sn), zinc (Zn), and zirconium (Zr). Some of these metals are found in only one of the salts in the category, but most are found as the metal for several in more than one compound. For example, Co is the metal for eight of the twenty salts in the category. The carboxylic acids range in chain length from a shorter C2 alkyl chain (acetate) or a C3 propionate (as shown in Fig. 1a) to the longest C18 stearate (Fig. 1d) and the acids have either straight chains, e.g., stearate (Fig. 1d) or branched chains, e.g., 2-ethylhexanoic (Fig. 1b) or neodecanoic

[1] This category also includes one acid with an aromatic ring (nonylphenol barium salt) and two with cyclic rings (Zn and Co naphthenates).

acids (Fig. 1c). The metal carboxylates are functionally similar and have the same ionizable substituents, the metal cation, and the carboxylic acid group (RCOOH). The metal carboxylates are primarily divalent compounds and have two carboxylic acid moieties per molecule. The metal carboxylate salts are designed to add metals to chemical reactions; therefore, they are designed to readily dissociate into the free metal and free acid. Dissociation constants have been measured for 18 of the 20 metal carboxylate compounds. Dissociation data is presented below. Because of the importance of the effect of ready dissociation in the characterization of the toxicity of these compounds, it is discussed at length below.

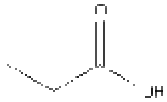
Dissociation Studies

One key characteristic of the compounds in the Metal Carboxylates Category is that they readily dissociate from an ion pair into free metal and free acid. They are found as partially dissociated products in the ambient environment (i.e., neutral pH). 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 all of the 20 metal carboxylates. 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.

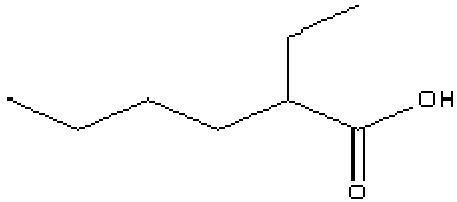
Dissociation studies have been conducted for 18 of the 20 compounds in the Metal Carboxylates Category. Results are presented in Table 1. Completion of the dissociation study with two aluminum stearate compounds was not possible due to low water solubility, although these compounds are also expected to readily dissociate (Crompton Corporation, personal communication). These studies 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 acids and metals to support the existing data for the salts within each subcategory and in the fulfillment of critical endpoints.

Dissociation is a reversible reaction, splitting the parent compound into two or more chemical species which may be ionic, but are not necessarily so. The dissociation studies presented here were conducted according to OECD Guideline 112. The process can be generally represented as equation #1. The

Figure 1: Structures of Representative Carboxylic Acids Found in Metal Carboxylates



a



b

c

d

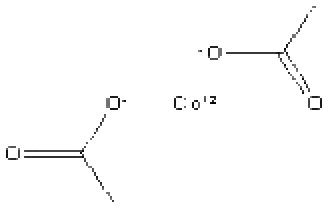
Table 1: Dissociation Constants for 20 Metal Carboxylates

Chemical	**CAS#**	**pKa Values (mean of 3)***			
		pKa1	pKa2	pKa3	pKa4
Cobalt Acetate	71-48-7	7.750*	4.910		
Propionic Acid, Calcium Salt	4075-81-4	6.758*	4.745		
Propionic Acid, Cobalt (2+) Salt	1560-69-6	7.583*	4.848		
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0	6.893			
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6	8.448			
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7	6.409			
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8	6.992			
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9	5.813	7.033	7.648	8.235
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0	5.088			
Naphthenic Acids, Cobalt Salt	61789-51-3	6.737	8.004		
Naphthenic Acids, Zinc Salt	12001-85-3	7.310	9.176		
Phenol, Nonyl, Barium Salt	28987-17-9	8.342*	6.805	5.618	
Neodecanoic Acid, Cobalt Salt	27253-31-2	6.517			
Fatty Acids, C9-13-Neo-Cobalt Salts	68955-83-9	5.964			
Cobalt Borate Neodecanoate Complexes	68457-13-6	6.405			
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4	5.818			
Aluminum Distearate	300-92-5	---**			
Cobalt Stearate	13586-84-0	7.498			
Barium Distearate	6865-35-6	6.706			
Aluminum Tristrearate	637-12-7	---**			

* For four compounds this is actually the pKb.

** The pKa values were not measured for two aluminium stearate compounds because the solubility was too low to be analyzed under the test guideline (OECD 112).

Figure 2: The Structures of Representative Metal Carboxylate Salts



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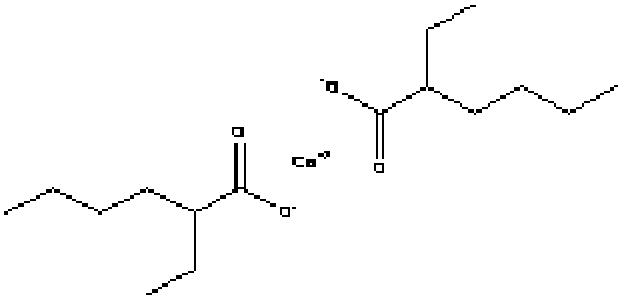

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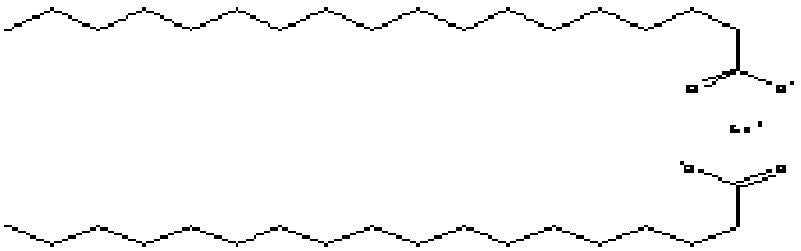


c

Equation #1

High pH Low pH

$$[RCOO^-]_x:[M^+]_x \;?\; [RCOO^-]_x + [M^+]_x \;?\; [RCOOH]_x + [MCl]_x$$

(salt) (Titrate with HCl ?) free acid and free metal

pKa and pH are equal when the parent compound (metal carboxylate salt) is 50% dissociated. The parent compounds, the metal carboxylate salts, are associated ionized molecules as shown in Figure 2. This figure shows three typical metal carboxylate salts with different chain lengths of the carboxylic acids: Co acetate (Fig. 2a), Co 2-ethylhexanoate (Fig. 2b), and Co stearate (Fig. 2c). Ionic charges are indicated for the acid and metal components of these salts (Figure 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 and corresponding free metal 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 constants reported in Table 1 indicate that all 18 compounds tested have pKa (pKb) values (pKa1) in the neutral range (5.088 to 8.448). This indicates that in the neutral pH range, significant portions of the metal carboxylates 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. This indicates that the absorption and any observed toxicity would be independent for the respective acid and metal when administered orally.

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 free acid, or that for a simple salt (e.g., the sodium salt), can to serve as a surrogate data for the acid component of respective metal carboxylates. Similarly, under these conditions, data for the metal ion can be represented by fate and toxicity data on 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).

Bioequivalency of Metal Carboxylates

Recent studies conducted to evaluate the "bioequivalency" (an estimate of bioavailability) of cobalt compounds, included three cobalt carboxylates and cobalt chloride. The solubility of these compounds in synthetic biological fluids (gastric juices, intestinal juices, several interstitial fluids, and cytosol) showed that these salts were completely dissociated and dissolved at gastric pH and cytosolic pH. The dissolution of these compounds ranged from 26.1% to 80.4 % of available cobalt at neutral pH (Table 2). The results for cobalt chloride and cobalt 2-ethyl-hexanoate were very similar at acidic and neutral pH. Cobalt neodecanoate and cobalt naphthenate showed similar levels of dissolution at acidic (gastric and cytosolic) pH, but smaller proportions of the metal component of these compounds were dissolved at neutral pH. The differences in dissolution for these metal carboxylates at neutral pH in synthetic body fluids could be related to differences in their dissociation constants (Table 1).

Table 2: Results of Extraction of Cobalt from Surrogate Biological Fluids

Matrix (pH)	**Maximum Solubility (% of available metal)**			
	$CoCl_2$	Co 2-ethyl-hexanoate	Co naphthenate	Co neodecanoate
Gastric pH (1.5)	>91.6	100	>85.7	100
Intestinal pH (7.4)	>79.4	50.8*	45.4*	30.8*
Alveolar pH (7.4)	>68	>59.6	35.4*	26.1*
Interstitial pH (7.4)	78.4	>80.4	40*	43.1*
Serum	>85	>66.9	42.9*	46.6*
Intracellular pH (4.5)	>89.6	100	>79.1	>78.1

* maximum extraction level at 72 hours
All data is taken from Stopford et al. (unpublished) Bioequivalency Testing of Cobalt Compounds. Conducted by Duke University Medical Center, Division of Occupational and Environmental Medicine for the Cobalt Development Institute.

These data are valuable for three reasons:

1. They confirm the prediction that these compounds would be expected to be completely dissociated in the gastrointestinal tract (low pH) and a substantial proportion of these compounds would be expected to be dissociated and bioavailable at neutral pH (7.4).

2. The fraction of the three cobalt carboxylates that is dissolved at acidic and neutral pH is very similar for different acid constituents with a range of molecular weights and chain lengths. This finding greatly strengthens the extrapolation of the results to the entire category.

3. The work by Stopford et al. (unpublished) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metals. Chlorides of the various metals have been emphasized during preparation of the attached robust summaries and are the preferred surrogate data for carboxylate salts.

Supporting Data for Dissociation Products

1. Data for the parent compounds (i.e., the metal carboxylate salts) are provided in robust summary format. A set of robust summaries for each of the 20 metal carboxylate compounds are provided an appendix to this document.

2. In addition, when available, data for the dissociation products (metals and acids) are provided within the parent robust summary in the "Remarks" section.

Consistent with discussions between the Metal Carboxylates Coalition (the Coalition) and the EPA, data for the dissociation products (metals and acids) are recognized as being essential to understanding the environmental fate and toxicological characteristics of the respective metal carboxylate salts. Data for each individual acid (free acid or Na, K or Ca salt) and each individual metal (free metal, metal chloride, other simple metal salt) are useful in characterizing the hazard of a metal carboxylate compound. These data are available for compounds being sponsored in the HPV Challenge Program, chemicals sponsored in other existing chemicals testing, e.g., program (ICCA, SIDS) or pesticidal chemicals registered under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). It is important to recognize that most of the compounds in the metal carboxylate category are a combination of relatively common acids and metals. These data are clearly delineated as supporting data for the respective acids and metals and robust summaries were not prepared for individual acids or metals. If robust summaries for acids were available through the HPV Program, they are provided as attachments to the salt robust summaries.

1
Acids

When available, robust summaries for respective acids have been provided as appendices to each set of robust summaries for each respective salt. For example, the robust summaries for 2-ethylhexanoic acid were made available to the Coalition. These data are summarized and referenced in the appropriate remarks sections for each data element in the robust summaries of the six 2-ethylhexanoate carboxylates. The 2-ethylhexanoic acid data is attached as Appendix 1 to each of six sets of robust summaries for the 2-ethylheaxanoate salts. Data for each of the acids is also summarized in Table III. Separate Robust summaries were not prepared by the Coalition for either individual metals or acids. Finally, because almost all of the acids are being sponsored under HPV Challenge or ICCA programs (e.g., neodecanoic acid, stearic acid, tall oil fatty acids). When this additional data for these acids becomes available, the Coalition will make a supplemental submission to EPA with data for these acids incorporated into the robust summaries for the compounds in the Metal Carboxylates Category.

Metals:

Data for most of the nine metals of interest are extensive. Rather than collect and review individual studies, the Coalition has relied upon well recognized and peer reviewed compendia (e.g., ATSDR Toxicological Profiles, WHO Environmental Health Criteria). Summarized data for the most appropriate forms of the metal (free metal or the chloride salt) are provided in the remarks section of the appropriate robust summary for each of the 20 metal carboxylates, as well as in tabular form in Table III. These well known compendia for metals are not provided with this submission, consistent with discussions with the EPA. These are readily available for EPA to review with this submission.

Summary

In summary, the key points relative to the Metal Carboxylates Category are:

- A common structure of RCOOH and a metal cation;
- Dissociation constants (pKa) in the circum neutral range (5.088 to 8.448);
    - Complete or nearly complete dissociation at gastric and cytosolic pH levels;
    - A moderate to high proportion of dissociation in the neutral pH range;
- General bioequivalency for salts with the same metal cation (for example, cobalt) and different acids or the chloride salt;

- Metal carboxylates have the same use pattern, to provide free metal ion to chemical reactions.
- Provision of data for the parent molecule or one or both of its dissociation products

SUBCATEGORIES

Rationale

The various carboxylic acids found in the 20 metal carboxylates in the Metal Carboxylate Category represent a range of chain lengths and other structural characteristics (e.g., branching, saturation, and the presence of ring substituents). These carboxylic acids can be grouped into six subcategories based on these structural characteristics and molecular weight (See Table 3 below), but they all have two things in common. They are all carboxylic acids and they are associated with a range of metals common to some or all of the subcategories.

Subcategories are listed in Table 3 and definitions are provided below with discussion of each subcategory and proposed testing. Testing needs for each subcategory are considered independently and are designed to allow each subcategory to stand alone. However, the Coalition believes that there is significant added value in evaluating these six subcategories as one overall category based on the common structural characteristics and ready dissociation as discussed previously.

Proposed Test Plan

The Coalition has taken a three pronged approach to category development for the metal carboxylates. First, the Coalition has collected and analyzed existing data for these twenty compounds. The existing data for the metal carboxylate salts have been summarized in robust summaries and ranked for reliability according to EPA Guidance.

As the second prong of the approach to category development, the Coalition has gathered existing data for the dissociation products, the respective metals and acids, and incorporated this data into the robust summaries and in the category justification for the metal carboxylate salts (as discussed above).

As the third prong, generation of additional data is proposed to support the Metal Carboxylates Category. This proposed testing program is outlined in Table I and the rationale provided below.

Table 3: List of Subcategories

Category 1 - Acetates/Propionates	***CAS#***
Cobalt Acetate	71-48-7
Propionic Acid, Calcium Salt	4075-81-4
Propionic Acid, Cobalt (2+) Salt	1560-69-6
Category 2 - 2-Ethylhexanoates	
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0
Category 3 - Naphthenates	
Naphthenic Acids, Cobalt Salt	61789-51-3
Naphthenic Acids, Zinc Salt	12001-85-3
Category 4 - Fatty Acids	
Neodecanoic Acid, Cobalt Salt	27253-31-2
Fatty Acids, C9-13-Neo- Cobalt Salts	68955-83-9
Cobalt Borate Neodecanoate Complexes	68457-13-6
Category 5 - Barium Nonyl Phenol	
Phenol, Nonyl, Barium Salt	28987-17-9
Category 6 - Stearates and Tall Oils	
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4
Aluminum Distearate	300-92-5
Cobalt Stearate	13586-84-0
Barium Stearate	6865-35-6
Aluminum Tristearate	637-12-7

Proposed testing by subcategory

Subcategory 1- Acetates and Propionates

Table 4: Subcategory 1: Acetates and Propionates	***CAS#***
Cobalt Acetate	71-48-7
Propionic Acid, Calcium Salt	4075-81-4
Propionic Acid, Cobalt (2+) Salt	1560-69-6

Subcategory 1 compounds (Table 4) have identical acid components, either acetate (Figure 2a) or propionate (Figure 1a). These acids are identical with the exception that propionic acid has one more carbon than acetic acid. The chain lengths of 2 or 3 carbons are small relative to the other carboxylic acids in the category. These materials dissociate to form propionic acid or acetic acid (that have similar physico-chemical and environmental fate characteristics) and the relevant metal salt (Co or Ca). The acids are readily soluble, being relatively small in molecular weight. With the shortest carbon chain lengths in the Category, these compounds, are more readily bioavailable and potentially more toxic than the remaining 17 metal carboxylates that have longer chains and larger molecular weights.

Existing data for the compounds in this subcategory and the related metals and acids are summarized in Matrix 1. In order to support this subcategory, the Coalition proposes to generate the following data:

<u>Physicochemical Properties</u>:

Melting point, boiling point, water solubility, and partition coefficient are proposed to be determined for Co acetate and Co propionate. Boiling point and partition coefficient data will be generated for Ca propionate.

<u>Environmental Fate Parameters:</u>

Adequate biodegradation data are currently available for the two acid components in this subcategory, or will be after the completion of HPV testing for acetic acid. To supplement this information, biodegradation data will be generated for Co propionate to determine the effect, if any, of cobalt on biodegradation of the compound under ambient conditions. . Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN) for all three members of the subcategory.

<u>Ecotoxicity:</u>

Sufficient data is available for the salt for Ca propionate and for the dissociation products of Co acetate and Co propionate. Acute aquatic toxicity testing on to

fish, daphnia and algae is proposed to be conducted with for Co propionate to confirm that under ambient environmental conditions (i.e., neutral pH), the compound is not more toxic than its dissociation products.(or to generate data under ambient conditions for comparison to those for its dissociation products.)This testing will insure that upper bound toxicity data are generated for this compound and for the subcategory as a whole.. Sufficient data is available for the salt for Ca propionate and for the dissociation products for Co acetate.

Human Health Effects:

No acute mammalian toxicity and genotoxicity studies are proposed. All data elements are addressed with existing data on the salt or the dissociation products. There is substantial existing data for Ca propionate, including data from higher tiered mammalian studies (Matrix 1). However, the repeated dose and developmental data studies are from secondary literature references and thus could not be directly rated for reliability, but are believed to be adequate based on the long history of use of this compound as a food additive and preservative the reliability was Unassignable. There is no reproduction study for Ca propionate. For Co acetate, the Coalition will rely upon the data for the dissociation products. The Co data is available and the acetic acid data for the higher tiered mammalian studies is being addressed by the Acetic Acids and Salts Panel (The American Chemistry Council). The Test Plan will be modified and a supplemental submission provided when the acetic acid data becomes available (see Test Plan matrix, Table I). The repeated dose data element is addressed for the Co propionate based on the dissociation products and the remaining higher tiered studies are considered representative of the subcategory.

Subcategory 2 - 2-Ethylhexanoate Salts

Table 5: Subcategory 2 – 2-Ethylhexanoates	***CAS #***
Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6
Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7
Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8
Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0

The second subcategory includes six metal salts of 2-ethylhexanoic acid (Table 5. Structures of the acids and a representative salts are shown in Figures 1b and 2b, respectively. The carboxylic acid, 2-ethylhexanoate, includes eight carbons and is a branched structure with an ethyl side chain on the second carbon. These branched compounds are substantially larger than those in subcategory 1 with a molecular weight range of 182 to 405 gm/M. With the exception of potassium, the metals in this subcategory are all divalent, i.e., are associated

with two 2-ethylhexanoic acid moieties, and the salts have a molecular weight range of 182 to 405 gm/M.

Available data are described in Matrix 2. In addition to the data available for the salt there is a complete set of robust summaries for the acid, 2-ethylhexanoate, which is being sponsored under the OECD SIDS program by the Oxo Process Panel of the American Chemistry Council. Summaries of available data for the metals for each respective salt are provided in Table II and Matrix 2. For this assessment, potassium and calcium have not been considered to be toxicologically significant and the potassium and calcium carboxylate salts are considered to have properties essentially the same as to the free acid.

The existing data for each 2-ethylhexanoate salt, the acid and the metals (with the exception of Ca and K) are shown in Matrix 2. In general, physicochemical property and environmental fate data are not available. The Coalition proposes to generate the following data:

Physicochemical Properties:

Generation of melting point, boiling point, solubility, and partition coefficient data are proposed for all six 2-ethylhexanoic acid salts (see Table I).

Environmental Fate Parameters:

Based upon demonstrated dissociation of these metal carboxylate salts and the refractory nature of the metals, biodegradation will depend primarily on the free acid. Data for biodegradation is proposed to be generated for the Zn and Sn 2-ethylhexanoate salts. These two salts were expected to represent a worst-case combinations of metal and acid for evaluating the subcategory as a whole. Since the acid (2- ethylhexanoate) has reliable biodegradation data, the Coalition will rely upon data for the acid alone to characterize the hazard of the potassium and calcium salts of 2-ethylhexanoate, based on the low order of toxicity for these metals. The remaining two salts are considered representative of the subcategory. Photodegradation and transport (fugacity) will be estimated using SAR models for all six compounds.

Ecotoxicity:

Reliable ecotoxicity data are not available for ecotoxicity for any of the salts in this subcategory, but are available for the 2-ethylhexanoic acid (Matrix 2). Extensive ecotoxicity data are also available for all of the metals. The Coalition believes that, in conjunction with new data to be generated on tin 2-ethylhexanoate, data for the parent acid and individual metals sufficient for hazard characterization of metal carboxylates in this subcategory (Matrix 2). Three ecotoxicity studies are proposed for the tin 2-ethylhexanoate salt. This

testing will insure that upper bound toxicity data are generated for this compound and for the subcategory as a whole under ambient pH conditions where complete dissociation may not occur. The remaining ecotoxicity values will be estimated using an SAR model (ECOSAR using new octanol water partition coefficient data to be generated). Although the existing ecotoxicity data for this subcategory is not especially reliable, the studies for the different compounds were performed by the same laboratory using the same procedures, and thus provide an indication of the relative toxicity of the compounds. The data for the acid and proposed ecotoxicity data generated on the tin salt plus estimated values using SAR models are expected to confirm the indications of relative toxicity within the subcategory.

Human Health Effects:

Existing data is available for mammalian acute (oral) toxicity and genotoxicity (*in vitro* and *in vivo*) for six of the 2-ethylhexanoate salts based on existing data for the salt and/or the dissociation projects (Matrix 2). Data are available for the higher tiered mammalian toxicity studies for all dissociation products of the six salts and the acid with the exception of the Zr 2-ethylhexanoate salt. For this compound, repeated dose data is available, but additional data on the developmental or reproductive toxicity of the metal are lacking. Because of this, and new data will be generated for the developmental and reproduction data elements for Zr 2-ethylhexanoate.

Subcategory 3 - Naphthenates

Table 6: Subcategory 3 - Naphthenates	***CAS #***
Naphthenic Acids, Cobalt Salt	61789-51-3
Naphthenic Acids, Zinc Salt	12001-85-3

The third subcategory consists of two compounds with naphthenic acid as the common “acid” for the Zn and Co naphthenates (Table 6). Zn naphthenate is considered the core chemical in this subcategory having reliable, existing data for most SIDS data elements. There is a substantial amount of existing data for the naphthenates, which is further supported by a nearly complete set of reliable studies for the copper salt, Cu naphthenate. This compound is not supported under the HPV Challenge Program, but has a FIFRA dossier[2]. Robust

[2] These studies were previously reviewed by the Office of Pesticide Programs to support the use of copper naphthenate under the FIFRA Deregistration Program. Because they did not exist, robust summaries for the Cu naphthenate studies were prepared by the Metal Carboxylates Coalition to facilitate comparison with Zn and Co naphthenate data. This is in contrast to acid data where robust summaries already existed, for the specific studies, and the Coalition did not want to rewrite or reinterpret studies or robust summaries already reviewed, or subject to future review, by the EPA as part of the HPV Challenge Program.

summaries have also been prepared for the copper salt (Matrix 3) and are provided with this submission per conversations with EPA. No additional data will be generated for the Cu salt. Data are also available for the naphthenic acid (and the sodium salt of naphthenic acid). All the existing data are summarized in Matrix 3.

To support this subcategory, the Coalition has proposed to generate the following additional data:

Physicochemical Properties

Data will be generated for partition coefficient for both Zn and Co naphthenates; and water solubility will be generated for Co naphthenate. Adequate data is available for the remaining physicochemical properties (see Matrix 3 and the Test Plan Matrix, Table I)

Environmental Fate Parameters:

Biodegradability will be determined for Co naphthenate (see Table 1). Adequate data is available for the Zn naphthenate. Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN) for both Co and Zn naphthenates.

Ecotoxicity:

No ecotoxicity testing is proposed for this subcategory. Adequate data are available for all three data elements for both the Co and Zn naphthenates, with the exception of aquatic plant toxicity for the Co salt, which are considered representative of the subcategory as shown in Matrix 3. Data are also available for the copper salt for these data elements (Appendix I of the Co and Zn Naphthenate Robust Summaries).

Human Health Effects:

Acute mammalian toxicity studies, genotoxicity (*in vitro* and *in vivo*) and higher tiered mammalian studies (i.e., repeated dose, reproduction, and developmental toxicity) are available for the core chemical Zn naphthenate and for the supporting chemical Cu naphthenate. Most of these data elements are also filled for the Co naphthenate with adequate data for the salt of the dissociation products; therefore, no additional studies are proposed for the chemicals in this subcategory (see Matrix 3 and Test Plan Matrix, Table I).

Subcategory 4 -: Neodecanoic and Fatty Acids

Table 7: Subcategory 5 - Neodecanoic and Fatty Acids	***CAS #***
Neodecanoic Acid, Cobalt Salt	27253-31-2
Fatty Acids, C9-13-Neo- Cobalt Salts	68955-83-9
Cobalt Borate Neodecanoate Complexes	68457-13-6

The neodecanoic acid compounds (C10) and the C9-13 neo fatty acids listed above (Table 7) comprise Subcategory 4. The structure of neodecanoic acid provided in Figure 1c is a branched chain with three methyl groups on the terminal carbon in the primary chain.

The data for theses Co (and Co, borate) salts are presented in Matrix 4. Data for the metals and acids are provided in Tables II and III respectively. To support this subcategory, the Coalition proposes to generate the following data:

Physicochemical Parameters:

Data for four physico-chemical property data elements, melting point, boiling point, solubility, and partition coefficient, will be generated with the exception of boiling point for neodecanoic acid Co salt, which is addressed with existing data.

Environmental Fate Parameters:

A biodegradation study will be conducted on Co borate neodecanoate complexes. There are already adequate existing biodegradation data for the acid dissociation products of the other two compounds in this subcategory. Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN) for all three compounds in this category.

Ecotoxicity:

Acute aquatic toxicity to fish, *Daphnia* and aquatic plants will be generated for neodecanoic acid, Co salt. Data generated for this salt will be considered representative of the entire subcategory.

Human Health Effects:

Acute toxicity, bacterial mutagenicity and a chromosome aberration data will be generated with neodecanoic acid, Co salt. These data will be used to represent the fatty acids, C9-13-neo- Co Salts, and Co borate neodecanoate complexes (see Table I). No higher tiered studies are required based on existing data for the dissociation products. Data on fatty acid, C9-C13, neo and neodecanoic acid are currently being generated under the HPV Challenge Program by ExxonMobil as

part of the Neo Acids C5-C28 Category. When they become available, data from these studies will be incorporated into the robust summaries used to support the Neodecanoic and Fatty Acids Subcategory.

Subcategory 5 - Barium Nonyl Phenol

Table 8: Subcategory 5 - Barium Nonyl Phenol	***CAS #***
Phenol, Nonyl, Barium Salt	28987-17-9

The fifth subcategory is a single compound, nonylphenol, Ba salt (Table 8). There is an extensive data set for the “acid” nonylphenol (Table III). This compound dissociates and the metal Ba is present only as a small proportion of the overall molecular weight (24%). Barium has a low order of toxicity (Table II); therefore, any observed toxicity of the salt would be expected to be due primarily to the nonylphenol moiety. This acid has an aromatic ring at the acid end of the chain, as well as a single straight alkyl (C9) chain substitution which may vary in length which and which may occur at one or more the positions on the aromatic ring.

Physicochemical Properties:

Melting point, boiling point, water solubility, and partition coefficient studies are proposed for nonylphenol, Ba salt.

Environmental Fate Parameters:

The biodegradation data element is filled using nonylphenol data (see Matrix 5 and Table I). Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN).

Ecotoxicity:

These data elements are filled based on data for the dissociation products.

Human Health Effects:

Dissociation of nonylphenol Ba salt (Table 1) has been demonstrated and all mammalian toxicity data elements are filled using existing data for the dissociation products.

Subcategory 6 - Stearates and Fatty Acids, Tall-Oils

Table 9: Subcategory 6 - Stearates and Fatty Acids, Tall Oils	***CAS #***
Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4
Aluminum Distearate	300-92-5
Cobalt Stearate	13586-84-0
Barium Stearate	6865-35-6
Aluminum Tristearate	637-12-7

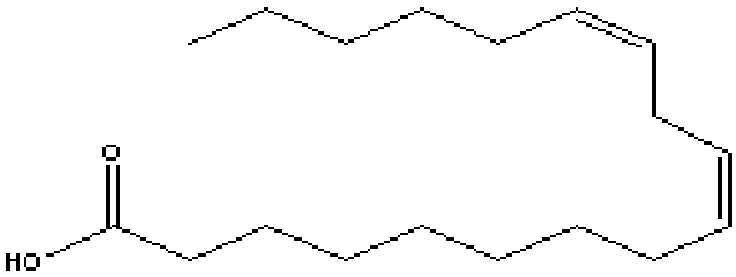
The sixth subcategory includes the metal carboxylates with stearates and fatty acids, tall-oils (Table 9) which contain primarily stearic (Fig. 3a), oleic (Fig. 3b), and linoleic (Fig. 3c) acids. These are the highest molecular weight compounds among the metal carboxylates with molecular weights ranging from 280.45 gm/M for fatty acid tall oil (linoleic) to 877.35 gm/M for Al tristearate. The metals in this subcategory are divalent or trivalent with a typical structure shown in Figure 2c (divalent Co stearate). To support this subcategory, the Coalition has relied on the fact that these compounds will dissociate and that the respective acid, such as stearate, is the chemical of interest. Dissociation was demonstrated and dissociations constants were reported for four of the six compounds in this subcategory. The exceptions were the two aluminum stearates, which had solubilities too low to allow analysis by the standard methods (OECD Guideline 112), but even these two compounds are expected to dissociate readily in water at neutral pH's and to be completely dissociated at the pH of the stomach (pH 1.2) similar to other metal carboxylates.

Stearic acid has a long history of use in foods and cosmetics. This compound is a member of the Aliphatic Acids Category and the Fatty Acids Tall Oil and Fatty Acid Related Substances Category that are being sponsored under the HPV Challenge Program.

Figure 3: Carboxylic Acids Found Subcategory 6

a

b



c

Likewise, tall oil fatty acids are part of the Tall Oil Fatty Acids and Related Substances Category that is also being sponsored in the HPV Challenge Program . Existing data for the salts in this subcategory and their associated acids and metals is summarized in Matrix 6.

The Metal Carboxylates Coalition is relying on the data for stearic acid and tall oil fatty acids to support this category and minimize unnecessary testing. When the Aliphatic Acids Category and Tall Oil Fatty Acids and Related Substances Category submission is made to the EPA under the HPV Challenge Program the robust summaries will become public domain. The Metal Carboxylates Coalition will then revise the current category development document to include the complete stearic acid and tall oil fatty acids data and will make a supplemental submission. The stearic acid salts will not be tested for these data elements, because stearic acid is a surrogate for the stearic acid salts based on known dissociation at neutral pH and at gastric pH.

Physicochemical Properties:

Melting point, boiling point, water solubility, and partition coefficient studies are proposed for all five metal carboxylate salts in this subcategory (Table 9 above) with the exception of existing data for melting point for Al distearate and Al tristearate.

Environmental Fate Parameters:

Biodegradation studies are proposed for Co stearate and Al tristearate, which are considered as to be representative of the subcategory. Since these compounds dissociate and the dissociated acid (stearic, oleic and linoleic acids) will be the moiety that degrades, the results would be expected to be the same for all five metal carboxylates in this subcategory. Photodegradation and transport (fugacity) will be calculated using SAR models (e.g., EPIWIN) for the six metal carboxylates in this subcategory.

Ecotoxicity:

Acute aquatic toxicity data elements, fish, *Daphnia* and aquatic plants, will be filled with data for the dissociation products including data for stearic acid and tall oil fatty acids that is being sponsored as part of the Aliphatic Acids Category and the Fatty Acids Tall Oil and Fatty Acid Related Substances Category. Because of the very low water solubility for the salts in this subcategory, a reproduction study (rather than an acute toxicity studies) is proposed for aquatic toxicity testing. Chronic *Daphnia* (21-d) studies are proposed for fatty acids, tall oil, Co salts and Co stearate, and are considered representative of the subcategory.

Human Health Effects:

Data elements for acute oral toxicity and *in vitro* genotoxicity will be filled using existing data for the dissociation products. The Coalition will rely on the results of the Aliphatic Acids Consortium submission to address the three higher tiered data elements for stearic acid and stearic acid salts. When they become available, these data will be incorporated into the Metal Carboxylates Test Plan.

SUMMARY

The robust summaries for twenty metal carboxylates and supporting information for the dissociation products are submitted to the EPA to fulfill commitments under the High Production Volume Chemicals (HPV) Program. These twenty compounds are divided into six subcategories based on structural features. Recent dissociation studies for 18 of 20 compounds and bioequivalency studies for Co salts show that these metal carboxylate salts are partially dissociated at neutral pH relevant to mobility in the environment and certain physiological compartments, and completely dissociated at gastric pH. The potential effects of these compounds on the environment and mammals can be addressed using data for the salt or data for the respective acid and/or metal. 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 physicochemical properties and environmental fate parameters. Based on the existing data, limited numbers of studies are proposed for ecotoxicity, acute mammalian toxicity, genotoxicity and the higher tiered mammalian studies (developmental and reproduction).

References

Stopford, W., J. Turner, D. Cappellini, and T. Brock. (unpublished) Bioequivalency Testing of Cobalt Compounds (Oct 15, 2002 Draft). Conducted by Duke University Medical Center, Division of Occupational and Environmental Medicine for the Cobalt Development Institute, Research Triangle Park, N.C.

Table I: Test Plan Matrix for the Metal Carboxylates Category

Table I: Test Plan Matrix	Physicochemical Prop.				Environmental Fate				Ecotoxicity			Human Health Effects					
	Melting point	Boiling point	Partition coefficient	Water solubility	Photodegradation	Dissociattion	Biodegradation	Fugacity	Acute fish	Acute invertebrate	Aquatic Plant toxicity	Acute oral toxicity	*In vitro* genotoxicity (bacterial)	*In vivo* genotoxicity (mammalian)	Repeated dose toxicity	Developmental toxicity	Reproductive toxicity
Subcategory 1																	
Cobalt Acetate	Test	Test	Test	Test	Calc	A	ADP*	Calc	ADP	ADP	ADP	A	A	A	ADP*	ADP*	ADP*
Propionic Acid, Calcium Salt	A	Test	Test	A	Calc	A	(A)	Calc	(A)	(A)	(A)	(A)	(A)	A	(A)	A	R
Propionic Acid, Cobalt (2+) Salt	Test	Test	Test	Test	Calc	A	Test	Calc	Test	Test	Test	ADP	ADP	ADP	ADP	R	R
Subcategory 2																	
Hexanoic Acid, 2-Ethyl, Potassium Salt	Test	Test	Test	Test	Calc	A	AO	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	ADP	ADP	ADP	ADP	ADP	ADP
Hexanoic Acid, 2-Ethyl, Ca Salt	Test	Test	Test	Test	Calc	A	AO	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	A	A	ADP	ADP	ADP	ADP
Hexanoic Acid, 2-Ethyl, Co (2+) Salt	Test	Test	Test	Test	Calc	A	R	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	A	A	A	ADP	ADP	ADP
Hexanoic Acid, 2-Ethyl, Zinc Salt	Test	Test	Test	Test	Calc	A	Test	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	A	A	ADP	ADP	ADP	ADP
Hexanoic Acid, 2-Ethyl, Zirconium Salt	Test	Test	Test	Test	Calc	A	R	Calc/ ADP	Calc/ ADP	Calc/ ADP	Calc	A	A	A	ADP	Test	Test
Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	Test	Test	Test	A	Calc	A	Test	Test	Test	Test	Test	A	ADP	ADP	ADP	ADP	ADP
Subcategory 3																	
Naphthenic Acids, Cobalt Salt	A	A	Test	Test	Calc	A	Test	Calc	A	A	R	A	A	R	ADP	R	R
Naphthenic Acids, Zinc Salt	A	A	Test	A	Calc	A	A	Calc	A	A	A	A	A	A	A	A	A
Subcategory 4																	
Neodecanoic Acid, Cobalt Salt	Test	A	Test	Test	Calc	A	ADP	Calc	ADP	ADP*	ADP*	Test	Test	Test	ADP*	ADP*	ADP*
Fatty Acids, C9-13-Neo-, Cobalt Salts	Test	Test	Test	Test	Calc	A	ADP	Calc	R	R	R	R	R	R	ADP*	ADP*	ADP*
Cobalt, Borate Neodecanoate Complexes	Test	Test	Test	Test	Calc	A	Test	Calc	R	R	R	R	R	R	ADP*	ADP*	ADP*
Subcategory 5																	
Phenol, Nonyl, Barium Salt	Test	Test	Test	Test	Calc	A	ADP	Calc	ADP	ADP	ADP	ADP	ADP	ADP	ADP	ADP	ADP
Subcategory 6																	
Fatty Acids, Tall Oil, Cobalt Salts	Test	Test	Test	Test	Calc	A	R	Calc	ADP*	Test/ CD	ADP*	ADP	ADP	ADP*	ADP*	ADP*	ADP*
Aluminum Distearate	A	Test	Test	Test	Calc	NA	R	Calc	ADP*	ADP*	ADP*	R	ADP	ADP*	ADP*	ADP*	ADP*
Cobalt Stearate	Test	Test	Test	Test	Calc	A	Test	Calc	ADP*	Test/ CD	ADP*	R	ADP	ADP*	ADP*	ADP*	ADP*

Table I: Test Plan Matrix for the Metal Carboxylates Category

Barium Stearate	Test	Test	Test	Test	Calc	A	R	Calc	ADP*	ADP*	ADP*	ADP	ADP	ADP*	ADP*	ADP*	ADP*
Aluminum Tristearate	A	Test	Test	Test	Calc	NA	Test	Calc	ADP*	ADP*	ADP*	ADP	ADP	ADP*	ADP*	ADP*	ADP*

Legend

Symbol	Description
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
(A)	Data rated as a Unassignable for reliability, but still considered adequate to address the given endpoint
ADP	Endpoint filled based on existing data for dissociation products (acid and metal)
ADP*	The Coalition relies upon acid data being generated under the HPV/ICCA Programs when metal data already exists.
NA	Not applicable due to physical/chemical properties
R	Endpoint requirement fulfilled using category approach.
CD	Chronic Daphnia
AO	Based on acid data only.

Table II. Summary of data available for metal and metal compounds contained in sponsored metal carboxylates.

Data Element	Aluminum Chloride & Al Compounds	Barium Chloride & Ba Compounds	Boric Acid & Boron Compounds	Cobalt Chloride & Co Compounds	Tin (Stannous) Chloride & Sn Compounds	Zinc Chloride & Zn Compounds	Zirconium Tetrachloride & Zr Compounds
Physicochemical Properties							
Partition Coefficient (log K_{OW})							
Water Solubility, mg/L					839,000 at 0°C	4.32 E6 at 25°C	
Environmental Fate and Pathways							
Photodegradation							
Stability in water							
Monitoring Data							
Transport (Fugacity)							
Biodegradation							
Bioconcentration							
Ecotoxicity							
Acute Fish LC50 (in mg/L for metal ion)	96-h LC50 = 27 mg Al/L for the mosquitofish and 8.6 mg Al/L for the rainbow trout. Exposures were to aluminum chloride.	48-h LC50 = 150 mg Ba/L for the brown trout; 96-h LC50 = 1,080 mg Ba/L for the mosquitofish and >1,000 for the mummichog, *Fundulus heteroclitus.*	LC50 values range from 14 to 3400 mg B/L for juvenile fish. Data suggest that rainbow trout and zebra fish are the most sensitive species.	96-h LC50 = 333 mg Co/L for the carp and 1406 mg Co/L for the rainbow trout	96-h LC50 is >0.035 mg Sn/L for the mud dab	96-h LC50 values: 0.45 to 2.25 mg Zn/L for the carp; 0.29 and 0.42 mg Zn/L for the bluegill; and 0.093 - 0.815 mg Zn/L for the rainbow trout. The range of reported 96-h LC50 values (n=15) for freshwater fish was 0.14 to 0.78 mg Zn/L for tests conducted with zinc chloride or zinc sulfate	96-hr LC50 >20 mg Zr/L for rainbow trout exposed to $ZrCl_4$. For zirconium oxychloride, the 96-h LC50 for the bluegill is 15 – 270 mg Zr/L and for the fathead minnow it is 18 –240 mg Zr/L. For fathead minnows exposed to the zirconium salt of sulfuric acid the LC50 is 141 to 45 mg Zr/L.
Acute Invertebrate EC50 (in mg/L for metal ion)	48-hr EC50 = 3.9 to 27 mg Al/L for *Daphnia magna*. Exposures were to aluminum chloride.	96-h LC50 values range from 46 mg Ba/L for a crayfish to 238 mg Ba/L for the scud, *Gammarus pulex*	48-h EC50 values for *Daphnia magna* exposed to boric acid are 133 and 226 mg B/L. For sodium tetraborate pentahydrate, the 96-h EC50 for *Daphnia magna* is reported to be> 182 mg/L (> 27 mg B/L).	48-h EC50 values reported for *Daphnia magna* exposed to cobalt chloride range from 1.11 to 5.6 mg Co/L	48-h EC50 values for *Daphnia magna* exposed to tin chloride are 19.5 and 55 mg Sn/L	48-h EC50 values = 0.33 to 0.80 mg Zn/L for *Daphnia magna* and 0.07 to 0.86 mg Zn/L for several crustaceans including 3 daphnids.	21-d EC50 = 2 mg Zr/L for *Daphnia magna* exposed to $ZrCl_4$
Aquatic Plants EC50 (in mg/L for metal ion)	Effects on algae *Scenedesmus quadricauda* occur at 1.5 to 2.0 mg Al/L in 4-d tests. Exposures were to aluminum chloride.	96-hr EC50 = 25 mg Ba/L for the duckweed, *Lemna minor*	The 96-h EC50 for the aquatic vascular plant, *Lemna minor*, is > 60 mg/L. The 72-h EC50 for the green alga, *Scenedesmus subspicatus*, is 34 mg/L.	96-h EC50 = 0.522 mg Co/L for *Chlorella vulgaris* exposed to cobalt chloride.	72-h EC50 values for tin chloride range from 0.21 to >0.5 mg Sn/L for *Skeletonema costatum.* The 8-d EC50 for *Ankistrodesmus falcatus* is 12 mg Sn/L.	96-h EC50 = 0.0447 mg Zn/L for *Selenastrum capricornutum.* 72-h EC50 = 0.142 mg Zn/L for *Skeletonema costatum.*	96-h EC50 = 2.6 mg Zr/L for *Selenastrum capricornutum* exposed to $ZrCl_4$
Mammalian Toxicity							
Toxicokinetics, metabolism, distribution	Absorption is poor, usually 0.1 to 1%	Oral absorption has ranged from 0.7% to 85.0% indifferent animal	Pharmacokinetic data indicate that boron, usually administered as	The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats.	Inorganic tin compounds are not readily absorbed after oral or inhalation	Absorption of zinc in lab animals can vary from 10-40%. Half-life	Less than 1% of the daily intake of zirconium of humans is excreted in

Table II. Summary of data available for metal and metal compounds contained in sponsored metal carboxylates.

Data Element	Aluminum Chloride & Al Compounds	Barium Chloride & Ba Compounds	Boric Acid & Boron Compounds	Cobalt Chloride & Co Compounds	Tin (Stannous) Chloride & Sn Compounds	Zinc Chloride & Zn Compounds	Zirconium Tetrachloride & Zr Compounds
distribution		85.0% indifferent animal studies.	usually administered as boric acid, is absorbed rapidly and virtually completely from the gastrointestinal tract and is rapidly excreted in the urine.	34% in the gut of rats. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine.	after oral or inhalation exposure. Absorption of Sn(II) from the G.I. tract is 2.85% in rats. Absorbed inorganic tin is excreted mainly in the urine.	10-40%. Half-life approx. 4-50 days in rats	humans is excreted in urine. Absorbed zirconium is either sequestered in the skeleton or excreted very rapidly.
Acute Oral LD50 (in mg/kg)	Rat: 380 to 3,730 mg/kg for aluminum chloride (equivalent to 77 to 753 mg Al/kg) with most values near 3,500 mg/kg; Mouse: 770 to 3,805 mg/kg for aluminum chloride (equivalent to 155 to 769 mg Al/kg).	Rat: 118 mg/kg for barium chloride (equivalent to 77.8 mg Ba/kg)	Rat & mouse: 400 to 700 mg B/kg for borax and boric acid; Guinea pig: 210 mg B/kg Dog, rabbit and cat: 250 to 250 mg B/kg	Rat: 19.1 to 85.5 mg Co/kg (cobalt chloride) and 55.4 to 72.5 mg Co/kg (cobalt sulfate). Mouse: 40.2 mg Co/kg (cobalt chloride) and 55.4 mg Co/kg (cobalt sulfate)	Lowest oral dose of stannous chloride that produced death: Rat: 473 mg Sn/kg; Mouse: 378 mg Sn/kg	Of the compounds zinc nitrate, zinc sulfate, zinc chloride and zinc acetate, zinc acetate was the most toxic, with oral LD50 values of 237 mg Zn/kg bw (rat) and 86 mg Zn/kg bw (mouse). The LD50 for zinc chloride in an oral exposure was reported to be 528 mg Zn/kg bw in rats and 605 mg Zn/kg bw in mice	Rat: 700 mg/kg for the tetrachloride salt (equivalent to 274 mg Zr/kg) and 3500 mg/kg for the oxychloride salt (equivalent to 1,792 mg Zr/kg).
Acute Inhalation LC50 (in mg/L)			The LC50 for sodium perborate tetrahydrate in rats is >74 mg/m^3.	Rat: 165 mg Co/m^3 as mixed cobalt oxides; > 10 mg Co/L for cobalt powder	Guinea pigs: exposure to tin (IV) chloride (3 mg/L for 10 minutes daily for several months) produced only transient irritation of the nose and eyes.	A 10-min exposure to 940 mg Zn/m^3 is lethal to rats	Severe, persistent interstitial pneumonitis has been produced in experimental animals exposed to airborne zirconium concentrations of 5 mg/m^3
Acute Dermal LD50 (in mg/kg)							
Skin Irritation	Solutions of 2.5 to 5.0 % aluminum chloride hexahydrate are mildly to moderately irritating to human skin when applied once daily for 3 days.		Boric acid and borax are mild to moderate skin irritants when applied to abraded skin.	Irritating	1% $SnCl_2$ produced pustules when applied to abraded rabbit skin, but not when applied to intact skin	Severe skin irritant to several species as a 1% ZnCl solution.	Certain zirconium salts (e.g. zirconium tetrachloride may cause irritation or caustic injury.
Eye Irritation					See acute inhalation above		Zirconium and its compounds are eye irritants
Repeated Dose Study	NOAEL = 62 mg Al/kg/day for a study with mice exposed to aluminum lactate via the diet; The LOAEL = 130 mg Al/kg/day based on neurobehavioral impairments.	NOAEL = 45 mg Ba/kg-day for female rats based on renal effects in the 1994 NTP study; LOAEL = 75 mg Ba/kg-day	NOAEL = 17.5 mg B/kg bw/day in a 2-year study with rats receiving boric acid or borax in the diet. LOAEL = 58.5 mg B/kg bw/day in this study.	LOAELs: 0.5 to 30.2 mg Co/kg/day (cobalt chloride) for oral exposures in rats	NOAEL = 32 mg Sn/kg/d for rats receiving stannous chloride via diet for 13 weeks (LOAEL = 95 mg Sn/kg/d). NOAELs = 63 and 164 mg Sn/kg/d for rats and mice, respectively, in 105 week feeding studies.	NOAELs were 53 to 565, and 104 mg Zn/kg/day for zinc sulfate fed in diet over 13 weeks to rats and mice, respectively. LOAEL = 12 mg Zn/kg/day as zinc chloride in rats exposed via water for 4 weeks.	NOAEL = 5 ppm in drinking water plus 2.6 ppm in feed for rats exposed over a lifetime to zirconium sulfate. No effects on rats and mice from exposure to 0.23 g Zr/kg/day of zirconium oxychloride.
Genetic Toxicity *in vitro*	Aluminum can cause genotoxicity under some circumstances, but has	Most *in vitro* genotox studies have found that barium chloride does not	Boric acid was not mutagenic in *Salmonella typhimurium* or in mouse	Cobalt compounds with a valence state of II, the form of cobalt released by	Negative results for stannous chloride with various bacterial systems;	In 11 *in vitro* studies with zinc chloride or zinc sulfate, negative results	Zirconium oxychloride and oxychloride hexahydrate are not

Table II. Summary of data available for metal and metal compounds contained in sponsored metal carboxylates.

Data Element	Aluminum Chloride & Al Compounds	Barium Chloride & Ba Compounds	Boric Acid & Boron Compounds	Cobalt Chloride & Co Compounds	Tin (Stannous) Chloride & Sn Compounds	Zinc Chloride & Zn Compounds	Zirconium Tetrachloride & Zr Compounds
	circumstances, but has given mostly negative results in several *in vitro* mutagenicity assays.	barium chloride does not induce gene mutations with or without metabolic activation.	*typhimurium* or in mouse lymphoma cells and did not induce chromosomal aberrations or sister chromatid exchanges in Chinese hamster ovary cells.	form of cobalt released by dissociation of cobalt salts, are reported to be generally non-mutagenic in bacterial assays, but increased frequency of genetic conversions have been reported in yeast. Cobalt compounds with a valence state of III were weakly mutagenic in bacterial systems.	various bacterial systems; however, mutagenic effects seen in some studies with mammalian cells.	sulfate, negative results were reported with the exception of two ambiguous results and one weakly positive result.	hexahydrate are not mutagenic in *Salmonella typhimurium*. $ZrCl_4$ is not mutagenic in tests with *S. typhimurium* or the SOS chromotest.
Genetic Toxicity *in vivo*	Aluminum chloride is clastogenic in mice bone marrow cells when dosed via i.p. injection.		Existing data suggest that genotoxicity is not an area of concern following exposure to boron compounds in humans.	Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells.	Stannous chloride was not genetically active in the host-mediated assay and did not cause chromosomal aberrations in rats when administered orally. Stannous chloride was non-mutagenic in rats in the Dominant Lethal Assay	Studies on the induction of chromosome aberrations in bone marrow cells harvested from animals exposed to elevated levels of zinc yield equivocal results.	Zirconium oxychloride has been shown to induce chromosomal abnormalities in bone marrow cells of mice after oral exposure.
Developmental Toxicity / Teratology	Oral exposure to aluminum compounds may induce skeletal variations and delayed ossification. Teratogenic changes have not been associated with gestational exposure to aluminum.	Developmental toxicity was not observed in a single-generation reproductive/ developmental toxicity study in which rats and mice were exposed to barium chloride in drinking water at levels up to 2,000 ppm.	Developmental toxicity of boron has been demonstrated in mice, rats and rabbits, with rats the most sensitive species. Doses of boric acid equivalent to 58 mg B/kg bw/day and above, when administered to pregnant rats for the whole of gestation, cause a high resorption rate and retardation of fetal development. The NOAEL for the rat, the most sensitive species, was 9.6 mg B/kg bw/day.	Rat fetus LOAEL = 5.4 mg Co/kg/day (cobalt chloride); based on stunted pup growth. No teratogenic effects observed. Another study in rats gave NOAEL of 24.8 mg Co/kg/day for cobalt chloride. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride	Inorganic tin compounds have not been shown to be fetotoxic.	The offspring of pregnant rats fed zinc carbonate (500 mg Zn/kg) did not demonstrate any increase in the incidence of malformations. Several developmental toxicity studies were conducted with zinc sulfate on mice, rats, hamsters and rabbits, in general accordance with OECD Guideline 414; however the form of the zinc sulfate was not specified. Depending upon the form that was used, the calculated NOAEL values ranged from 6.8 mg Zn/kg bw for the mouse to 35.2 mg Zn/kg bw for the hamster.	In mice, offspring of dams who received zirconium during pregnancy had long-lasting behavioral changes.
Reproductive Toxicity	Reproductive success was not affected in a three-generation study with mice exposed to 49 mg Al/kg/day in drinking water and base diet. No reproductive effects were	Reproductive toxicity was not observed in a single-generation reproductive/ developmental toxicity study in which rats and mice were exposed to barium chloride in	Effects on reproductive organs occur in both males and females, but at higher levels in females. Effects on fertility were seen in rats and mice. Testicular lesions have	Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water.	Tin(II) chloride was reported to cause testicular degeneration in rats after prolonged feeding (1.5 to 9.2 mg Sn/kg/d for 13 weeks). Histopathological	Rats fed zinc chloride daily over an 8 week period demonstrated altered sperm chromatin structure with a LOAEL of 25 mg Zn/kg/d. The LOAEL for serious	Small fractions of zirconium were absorbed in female rats by the oral route, and the metal seemed to concentrate in the ovaries and produce hypervascularization.

Table II. Summary of data available for metal and metal compounds contained in sponsored metal carboxylates.

Data Element	Aluminum Chloride & Al Compounds	Barium Chloride & Ba Compounds	Boric Acid & Boron Compounds	Cobalt Chloride & Co Compounds	Tin (Stannous) Chloride & Sn Compounds	Zinc Chloride & Zn Compounds	Zirconium Tetrachloride & Zr Compounds
	reproductive effects were observed in pregnant Swiss Webster mice that consumed 250 mg al/kg/day as aluminum lactate throughout gestation and lactation. An increased incidence of resorptions occurred in mice that were gestationally exposed to aluminum chloride by gavage, but no reproductive effects were found in rats similarly exposed to aluminum chloride, hydroxide, or citrate.	barium chloride in drinking water at levels up to 2,000 ppm.	Testicular lesions have been observed in rats, mice, and dogs administered boric acid or borax in food or drinking water in a number of studies. The lowest NOAEL for boric acid was based upon testicular effects (reduction in sperm count, inhibition of spermiation, and testicular atrophy) in male rats was reported to be 17 mg B/kg bw/day.	the diet or drinking water. Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks	Histopathological degeneration was seen in a few animals who were treated for 9 weeks at 30.5 mg Sn/kg/d and then sacrificed because of their moribund physiological state.	LOAEL for serious reproductive effects in female rats was 200 and 250 mg Zn/kg/d from exposure to zinc sulfate and zinc carbonate, respectively, in the diet.	hypervascularization.
Other Mammalian Toxicity Studies	Aluminum and aluminum compounds are not known to cause cancer in humans and none of the studies conducted on animals showed aluminum to be carcinogenic.	Oral exposure studies in rats and mice did not show significant increases in tumor incidences following chronic exposure to barium compounds for up to two years. Based on the available weight of evidence, barium is considered not likely to be carcinogenic to humans by oral exposure.	A 2-year feeding study showed no evidence of carcinogenicity in mice. There was no evidence of boric acid-related carcinogenicity in rats. Boron is classified by the US EPA as a Group D chemical (not classifiable as a human carcinogen).	The U.S. National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals.	Long-term bioassays with rats and mice exposed to stannous chloride in their diet and drinking water failed to produce any increase in incidence of tumors or the incidence of tumors was not clearly related to the administration of stannous chloride.	There is no adequate experimental evidence indicating that zinc salts administered orally or parenterally are tumorigenic.	Not classifiable as a human carcinogen. Rats administered 5 ppm of zirconium sulfate in drinking water for their entire lifetime did not have an increased incidence of tumors.

Table III. Summary of data available for carboxylic acids contained in sponsored metal carboxylates

Data Element		Acetic Acid	Propionic Acid	2-Ethyl Hexanoic Acid	Neodecanoic Acid	Fatty Acids, C9-C13 Neo	Naphthenic Acids	Phenol, Nonyl	Fatty Acids, Tall Oil	Stearic Acid
1	**Substance Information**									
1.0	CAS No.	64-19-7	79-09-4	149-57-5	26896-20-8	68938-07-8	1338-24-5	25154-52-3	61790-12-3	57-11-4
1.1	Molecular Formula	$C_2H_4O_2$	$C_3H_6O_2$	$C_8H_{16}O_2$	$C_{10}H_{20}O_2$	$C_9H_{18}O_2$ to $C_{13}H_{26}O_2$	Varies	$C_{15}H_{24}O$	$C_{18}H_{34}O_2$ (oleic) $C_{18}H_{32}O_2$ (linoleic)	$C_{18}H_{36}O_2$
1.2	Molecular Weight	60.05	74.08	144.22	172.27	158.24 to 214.35		220.36	282.47 (oleic); 280.45 (linoeic)	284.49
1.3	Structural Form									
2	**Physicochemical Properties**									
2.1	Melting Point (°C)	16.6	22	-118	48.1			24.5; 42		69.7
2.2	Boiling Point (°C)	117.9	141	228	252.1		132 to 243	290 to 302	160 to 210	376 - 383
2.3	Density		0.992				0.982			0.9408
2.4	Vapor Pressure		5 hPa	1.3×10^{-3} hPa				0.0000455 hPa		1.0 hPa
2.5	Partition Coefficient (log K_{OW})	-0.17	0.25 to 0.33	3.0 est.	3.8	3.4 to 5.4 est.		3.3; >3.8; 5.76	4.4 to 8.3 @pH 2; 3.5 to 7.4 @pH 7.5	8.2
2.6	Water Solubility (mg/L)	1×10^6	1×10^6	1,111 est. 25 IUCLID	80	2.3 to 210.5 est.		6.35	0.011 est.(oleic); 0.037 est (linoleic)	0.6 measured; 0.0035 est.
3	**Environmental Fate and Pathways**									
3.1.1	Photodegradation		50% after 4.7 years							
3.1.2	Stability in water									
3.2.1	Monitoring Data									
3.3.1	Transport (Fugacity)									
3.5	Biodegradation		95% in 10 d	Yes	11% in 28 days	2.3% in 28-d	Na salt: 50% in 24 d	7% in 28 d (Sturm); 78% in 40 d (BOD)	50% in 7 d; 56% in 28 d	72% in 28 d
3.7	Bioconcentration									
4	**Ecotoxicity**									
4.1	Acute Fish LC50 (mg/L)		67 to 85	70	37.2 to 181		5.6 to 16.3	0.13 5 to 0.95	10 to 20	> 1000
4.2	Acute Invertebrate EC50 (mg/L)		23 to 50	85	47 (*Daphnia*) 25 (*Acartia*.)		4.8 (calcium naphthenate, for copepod)	0.14 (*Daphnia*) 0.043 (Mysid)	55.7 (*Daphnia*)	> 0.09 (solubility limit; *Daphnia*)
4.3	Aquatic Plants EC50 (mg/L)		43 to 46	41			30.5 to 80.5 (*Navicula*)	0.027 to 0.323	0.8 to 9.0	> 1016
5	**Mammalian Toxicity**									
5.0	Toxicokinetics, metabolism, distribution		Is a normal intermediary metabolite in animals and humans	Approx. 75% of the oral dose excreted in urine within 24 h				10-20% of absorbed dose bioavailable; absorbed dose widely distributed in body		

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Data Element		Acetic Acid	Propionic Acid	2-Ethyl Hexanoic Acid	Neodecanoic Acid	Fatty Acids, C9-C13 Neo	Naphthenic Acids	Phenol, Nonyl	Fatty Acids, Tall Oil	Stearic Acid
5.1.1	Acute Oral LD50 (mg/kg)		2,600 – 4,290 (rat)	1,600 – 3,200 (rat)	2,000 – 3,450 (rat)		3,000; 6,420 (rat); 3,550 (Na salt)	1,000 – 2,000 (rat)	>10,000	> 2000 (rat)
5.1.2	Acute Inhalation LC50 (mg/L)		>4.9 (rat)	>2.4 (rat)	> 3.0 mg/L; > 73 ppm; > 511 mg/m^3					
5.1.3	Acute Dermal LD50 (mg/kg)		500 (rabbit)	<5 ml/kg (guinea pig)	>3,640 (rat); > 3160 (rabbit)			>2,000 (rabbit)		
5.2.1	Skin Irritation		Severe (G. pig)	Slight to moderately irritating	Non-irritating (rabbit)			Irritant		
5.2.2	Eye Irritation		Mild to severe	Severely irritating	Irritant			Irritant		No irritation to mild irritation
5.4	Repeated Dose Study (NOAEL)		NOAEL = 2,000 mg/kg/d in a 90-d dog study; NOAEL = 1,320 mg/kg/d in a 1-yr rat study on the sodium salt	NOAEL = 300 mg/kg/d in a 13-w rat study; NOEL = 65 mg/kg/d	NOAEL = 50 ppm in a 3 month feeding study (30% preparation); NOAEL = 30 mg/kg/d in a 13-w oral dog study		NOAEL = 6 mg/kg/d in a rat 90-d oral study	NOAEL = 100 mg/kg/d for rat in a 28-d study; NOAEL = 50 mg/kg/d for rat in a 90-d study	NOAEL = 15% in diet for 28-d rat feeding study; NOAEL = 5% in diet or approx. 2,500 mg/kg/d in a 90-d rat study	LOAEL = 3000 ppm in diet in a rat 30-w feeding study (based on mortality)
5.5	Genetic Toxicity in vitro	Negative, non-clastogenic	Negative	Negative	Negative			Negative	Negative	Negative
5.6	Genetic Toxicity in vivo		Negative	Negative				Negative		
5.8.2	Developmental Toxicity / Teratology (offspring)	Rabbit NOEL= 1600 mg/kg/day		Rat NOEL = 100 mg/kg/d; Rabbit NOEL = 250 mg/kg/d	See result for reproduction			Fetus NOAEL = 300 mg/kg		
5.8.3	Reproductive Toxicity			NOEL = 100 mg/kg in a rat one-generation study	NOEL = 1500 ppm in a rat three generation study		No adverse effects in male rabbits over 10 wks from dermal exposure to an overbased calcium naphthenate in mineral oil	LOEL = 15 mg/kg; NOEL not found in a 3 generation rat study.	NOEL = 10% in diet in a rat two generation study	
6.0	Other Mammalian Toxicity Studies		Precancerous changes in stomachs of rats fed 4% (2640 mg/kg/d) in diet over lifetim e		Not found to produce skin sensitization.			Estrogenic in several different assays		

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

ROBUST SUMMARIES

For the

METAL CARBOXYLATES CATEGORY

Prepared by

MorningStar Consulting, Inc.

on behalf of

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

DECEMBER 20, 2002

LIST OF ROBUST SUMMARIES

Robust Summary #	***Sponsored Chemical***	***CAS#***
1	Cobalt Acetate	71-48-7
2	Propionic Acid, Calcium Salt	4075-81-4
3	Propionic Acid, Cobalt (2+) Salt	1560-69-6
4	Hexanoic Acid, 2-Ethyl, Potassium Salt	3164-85-0
5	Hexanoic Acid, 2-Ethyl, Calcium Salt	136-51-6
6	Hexanoic Acid, 2-Ethyl, Cobalt (2+) Salt	136-52-7
7	Hexanoic Acid, 2-Ethyl, Zinc Salt	136-53-8
8	Hexanoic Acid, 2-Ethyl, Zirconium Salt	22464-99-9
9	Hexanoic Acid, 2-Ethyl, Tin (2+) Salt	301-10-0
10	Naphthenic Acids, Cobalt Salt	61789-51-3
11	Naphthenic Acids, Zinc Salt	12001-85-3
12	Neodecanoic Acid, Cobalt Salt	27253-31-2
13	Fatty Acids, C9-13-Neo- Cobalt Salts	68955-83-9
14	Cobalt Borate Neodecanoate Complexes	68457-13-6
15	Phenol, Nonyl, Barium Salt	28987-17-9
16	Fatty Acids, Tall-Oil, Cobalt Salts	61789-52-4
17	Aluminum Distearate	300-92-5
18	Cobalt Stearate	13586-84-0
19	Barium Distearate	6865-35-6
20	Aluminum Tristrearate	637-12-7

1.0 SUBSTANCE INFORMATION

Generic Name	:	Cobalt acetate
Chemical Name	:	Cobaltous acetate
CAS Registry No.	:	71-48-7
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$Co(C_2H_3O_2)_2$
Molecular Weight	:	177.03
Synonyms and Tradenames	:	Acetic acid, cobalt(2+) salt Cobalt diacetate
References	:	

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value : at °C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value : hPa at °C
Decomposition :
Year :

GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products**:
Acid: Acetic Acid (CAS 64-19-7) Log Kow = -0.17 (see Appendix 1)
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products**:
Acid: Acetic acid (CAS 64-19-7) Solubility is50 g/L @20°C (App. 1)
Reliability :
Reference :

2.7 FLASH POINT

Type :
Guideline/method :

Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic acid (94-19-7) calculated value of ~ 50% after 21 days. **Metal:** NA
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKb	:	7.75 and 4.91 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Cobalt (II) acetate (399973-10G), lot number 04119D0, received from Aldrich Chemical Company. Light purple powder, purity of 99.995+%.
Approximate water solubility	:	14,000 mg/L, as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of cobalt acetate were prepared at a nominal concentration of 0.01 moles/L by dissolving 0.1770 grams of the test substance in 100 mL degassed water (ASTM Type II). Each sample was titrated against 0.1 N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence

point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.

Result : Mean (N = 3) pKb values were 7.75 (SD = 0.0610) and 4.91 (SD = 0.0389) at 20°C

Remark : The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of cobalt acetate, Wildlife International, Ltd. Study No. 534C-112, conducted for the Metals Carboxylate Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration :
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Level I fugacity modeling with acetic acid (CAS 64-19-7) provided estimated partitioning to respective compartments of: 26.9% (air), 73.1% (water), 0.044% (Soil), 97.2 x 10^{-4}% (sediment), 3.04 x 10^{-5}% (suspended sediment) and 2.47 x 10^{-6}% (fish) (see Appendix 1).
Metal: NA
Reliability :
Reference :

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %
Control substance	:	
Kinetic	:	% %
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Acetic acid (94-19-7). Readily biodegradable. 99% reduction after 7 days in sewage treatment medium (see Appendix 1). **Metal:** NA
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
LC0 :
LC50 :
LC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Acetic acid (CAS 64-19-7) The 96-h LC50 is reported as 75.0 mg/L for *Lepomis macrochirus* and 251 mg/L for *Gambusia affinis* Acetic acid

Metal: The reported 96-h LC50 is 333 mg Co/L for *Cyprinus carpio* and 1,406 mg Co/L for *Onchorynchus mykiss* (ECOTOX data base).).
Reliability :
Reference :

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
EC0 :
EC50 :
EC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The 24 hour EC50s for *Daphnia* exposed to acetic acid (CAS 64-19-7) under static conditions ranged from 47.0 mg/L to 95.0 mg/L and the 48 hour EC50 was reported as 65.0 mg/L. When water was neutralized prior

to introducing the organisms the EC50 was 6,000 mg/L. (see Appendix 1).
Metal: The reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base).

Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The toxicity threshold for *Scenedesmus quadracauda* is reported as 4,000 mg/L after an 8-d exposure. Growth inhibition was the most sensitive measure of effect. (see Appendix 1).
Metal: The reported 96-h EC50 for *Chorella vulgaris* is 0.522 mg Co/L (ECOTOX data base).

Reliability :
Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** **Metal:** Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. Clin. Tox. 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Single dose
Guideline/Method	:	
Species	:	Rat

Strain	:	Wistar
Sex	:	Both male and female
Number of animals	:	5 per sex
Vehicle	:	Compound was administered either in distilled water or as a suspension of an Ultra-Turrax in a 1% carboxymethylcellulose solution.
Doses	:	250, 375, 560, 840, and 1260 mg/kg
LD50	:	503 mg/kg based on the weight of anhydrous compound 708 mg/kg based on the weight of the tetrahydrate compound 168 mg/kg based on the weight of cobalt(II) ion
Year	:	1981
GLP	:	
Test substance	:	Cobalt(II) acetate tetrahydrate; purity = 99%
Method	:	Gastric intubation
Method detail	:	Signs of reactions and deaths were recorded for 10 days, and the rectal temperature was measured in all surviving rats 1.5, 24, and 48 hours after administration of the compound.
Result	:	Respiratory disturbances were apparent before death. Body temperature was also reduced after administration.
Remark	:	Eight different cobalt(II) compounds were included in this study including cobalt chloride, cobalt bromide, cobalt fluoride and cobalt sulfate. Calculated on the basis of the cobalt(II) ion, the acute oral toxicities of the cobalt compounds tested were similar with LD50 values ranging from 91 to 168 mg Co/kg. Except for the bromide and fluoride compounds, which showed a somewhat higher acute toxicity, the contribution of the cation to the toxicity of the compound was negligible compared with that of the cobalt anion. The mouse LD50 for cobalt acetate is reported as 28 mg/kg when administered intravenously. (Venugopal and Luckey1978 cited in the Hazardous Substance Databank (HSDB)) **Supporting data for dissociation products:** **Acid:** The mouse LD50 for acetic acid (CAS 64-19-7) is reported as 4960 mg/kg b.w. (see Appendix 1) **Metal:** Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg $CoCl_2$/kg bw (equivalent to 19.8 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 46.7 to 61.2 mg Co/kg b.w. (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 46.7 mg Co/mg b.w. when expressed as metal (ATSDR Sept 2001 Draft).
Reliability	:	(2) Reliable with restrictions.
Reference	:	Speijers, G.J.A., E.I. Krajnc, J.M. Berkvens, and M.J. van Logten. 1982. Acute oral toxicity of inorganic cobalt compounds in rats. Food Chem. Toxicol., 20:311-314.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	

Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Acetic acid (94-19-7) has a reported inhalation LC50 of 11.0 mg/L in rats exposed for four hours. In mice the 1.0-h LC50 was 5,620 mg/L (see Appendix 1).
Metal: The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m3 as mixed cobalt oxides. (ASTDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was > 10 mg/L (IUCLID, 2000).
Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The dermal LD50 for acetic acid (94-19-7) to the rabbit is reported as 1060 mg/kg b.w.(see Appendix 1).
Metal: Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :

Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Metal:** Cobalt is reported to be irritating to the skin (IUCLID, 2000).
Reliability	:	
Reference	:	

5.2.2 EYE IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	

Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Rats dosed with 0.5 ml of a 3.0% solution of acetic acid (CAS 64-19-7) 3 times weekly for 8 months did not induce tumors although hyperplasia in the esophagus and forestomach was observed in exposed rats. In a parallel treatment group treatement with a known carcinogen NSEE did resulty in tumors. The esophagus and forestomach showed pre-neoplastic lesions, benign tumors, carcinomas, and squamous cell cancer. Treatment with acetic acid and NSEE combined resulted in increased levels of benign and malignant tumors, carcinomas in the esophagus. (see Appendix 1).
Metal: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Mutagenicity
Guideline/method : *Salmonella*/Microsomal Mutagenicity Assay
System of testing : Bacteria
Species : *Salmonella*
Strains : 5 (not specified)
Test concentrations : 0.03 to 10.0 mg/plate
Cytotoxic concentr. : Not specified
Metabolic activation : No
Year : 1987
GLP : Not specified
Test substance : Cobalt acetate
Method :
Method detail :
Result : Very weak to weak mutagenicity was detected at 10.0 mg/plate in three of five tester strains, but none was observed in any strains at lower levels (3.3, 0.33, and 0.3 mg/plate).
Remark : **Supporting data for dissociation products:**
Acid: Acetic acid (CAS 94-19-7) is negative in a bacterial reverse mutation assay with and without activation using strains TA 98, TA 100, TA1535 and TA1538. The same results were observed in a study using TA 98, TA 100,

TA1535 and TA 97 or TA1538. This study was negative with and without activation. In a third study acetic acid and as sodium and zinc salts showed no evidence of mutagenicity using *Salmonella typhimurium* with and without activation (see Appendix 1). In a non-bacterial *in vitro* study with Chinese hamster ovary K1 cells, acetic acid was not clastogenic at concentrations close to those showing cytotoxicity.(see Appendix 1).
Metal: Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be non-mutagenic in bacterial assays (ATSDR Sept 2001 Draft), but cobalt compounds with a valence state of III were weakly mutagenic.

Reliability : (2) Reliable with restrictions. Basic information available in an abstract only.
Reference : Turoczi, L.J., M. Bauzon, and L. Kocur. 1987. A genotoxic analysis of cobaltous acetate using the Salmonella mutagenicity assay and the mouse micronucleus test. Abstract 284. Environ, Mutagen. Vol 9, Suppl 8, pg 109.

Type : Mutagenicity (cell transformation, viral enhanced)
Guideline/method :
System of testing : Adenovirus transformation in hamster embryo cells
Species : Syrian hamster (host); Simian adenovirus SA7 (virus)
Strain :
Test concentrations : Not specified
Cytotoxic concentr. : Not specified
Metabolic activation :
Year : 1979
GLP : Not specified
Test substance : Cobalt acetate
Method :
Method detail :
Result : Cobalt acetate at a concentration of 0.2 mM enhanced transformation of the SA7 adenovirus by a factor or 7.2-fold suggesting that it is potentially mutagenic.
Remark :
Reliability : (2) Reliable with restrictions.
Reference : Castro, B.C., J. Myers, and J.A. DiPaolo. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 39: 193-198.

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method : Mouse micronucleus test
Species : Mouse
Strain : Not specified
Sex : Not specified
Route of admin. : I.P. injection
Exposure period :
Dose : 33 mg/kg
Year : 1987
GLP : Not specified
Test substance : Cobaltous acetate
Method :
Method detail :
Result : Nonmutagenic (Note slight paralysis and related difficulties were seen in mice exposed at 100 mg/kg)
Remark : **Supporting data for dissociation products:**

Acid:
Metal: Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in a range of mammalian systems. For example, increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (NOEL) (ATSDR Sept 2001 Draft).

Reliability : (2) Reliable with restrictions. Basic information available in an abstract only.

Reference : Turoczi, L.J., M. Bauzon, and L. Kocur. 1987. A genotoxic analysis of cobaltous acetate using the Salmonella mutagenicity assay and the mouse micronucleus test. Abstract 284. Environ. Mutagen. Vol 9, Suppl 8, pg 109.

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Teratogenicity
Guideline/method	:	Egg injection
Species	:	Chicken
Strain	:	Single-Comb White Leghorn
Sex	:	
Route of admin.	:	Injection through yolk and air cell
Exposure period	:	Through hatching
Frequency of treatment	:	Single treatment at either preincubation (0 hr) or fourth day (96 hr)
Duration of test	:	Through hatching
Doses	:	Up to 2.5 mg/egg
Control group	:	Yes (vehicle only)
NOAEL maternal tox.	:	Not applicable
NOAEL teratogen.	:	2.5 mg/egg
Other	:	LD50 = 0.10 mg/egg for injection into air cell at 0 hr
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	Cobaltous acetate
Method	:	
Method detail	:	Water used as vehicle for injection
Result	:	Not found to be teratogenic to chicken embryos up to a lethal level
Remark	:	Results are consistent with those of Ferm and Carrpenter (1968) who found that cobaltous acetate tetrahydrate at a dose of 5 mg/kg did not induce embryocidal or teratogenic effects when administered alone to golden hamsters. Ferm, V.H. and S.J. Carpenter. 1968. The relationship of cadmium and zinc in experimental mammalian teratogenesis. Lab Invest. 18:429-432.

Supporting data for dissociation products:
Acid: In 3 developmental studies with CD1 mice, Wistar rats, and Dutch-belted rabbits result showed no effects of acetic acid (CAS 64-19-7) on nidation or on maternal or fetal survival at doses up to 1600 mg/kg b.w./day (see Appendix 1).
Metal: In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride

growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).

Reliability : (2) Reliable with restrictions. Method is for screening purposes only.

Reference : Verrett, M.J., W.F. Scott, E.F. Reynaldo, E.K. Alterman, and C.A. Thomas. 1980. Toxicity and teratogenicity of food additive chemicals in the developing chicken embryo. Toxicol. Appl. Pharmacol. 56: 265-273.

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :

Remark : **Supporting data:**
Acid:
Metal: Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).

Reliability :
Reference :

6.0 OTHER INFORMATION

6.1 CARCINOGENICITY

The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). “No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt.” (ATSDR Sept 2001 Draft).

Note: Appendix I refers to the IUCLID profile for Propionic acid

1.0 SUBSTANCE INFORMATION

Generic Name	:	Propionic acid, calcium salt
Chemical Name	:	Propionic acid, calcium salt
CAS Registry No.	:	4075-81-4
Component Cas Nos.	:	
EINECS No.	:	223-795-8
Structural Formula	:	$C_6H_{10}CaO_4$
Molecular Weight	:	186.2226
Synonyms and Tradenames	:	Calcium dipropionate; calcium propionate; calcium propanoate; propanoic acid, calcium salt; Bioban-C; Luprosil Spezial; Mycoban
Reference	:	http://www.chemfinder.com; MSDS dated 6/6/01 prepared by Kemin Industries, Ltd.; MSDS as cited in IUCLID (2000). IUCLID Dataset. European Chemicals Bureau, European Commission. Dataset for Calcium Dipropionate, 2/18/2000. [Subsequently referenced as IUCLID (2000)]

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	Thermal decomposition at ca. 245°C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Melting point for propionic acid is reported to be 22.4°C (See Appendix I: 2.1)
Result	:	
Reliability	:	[4] Not assignable. Only secondary reference
Reference	:	MSDS as cited in IUCLID (2000)

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable.
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	**Supporting data for dissocation products:** **Acid:** Boiling point for propionic acid is reported to be 140.7 – 141.6°C (See Appendix I: 2.2)
Remark	:	
Reliability	:	
Reference	:	MSDS dated 6/4/01, prepared by Kemin Industries, Inc.

2.3 DENSITY

Type	:	Bulk density
Guideline/method	:	
Value	:	ca. 400 kg/m^3 at °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Density for propionic acid is reported to be 0.992 g/cm^3 at 20°C (See Appendix I: 2.3)
Reliability	:	[4] Not assignable. Only secondary reference
Reference	:	MSDS as cited in IUCLID (2000)

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	Not applicable
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Vapor pressure for propionic acid reported to be 5 hPa at 20°C (See Appendix I: 2.4)
Reliability	:	
Reference	:	MSDS dated 6/4/01, prepared by Kemin Industries, Inc.

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Log Pow for propionic acid reported to be 0.25 – 0.33 (See Appendix I: 2.5)
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method		
Value	:	260 g/L at 20°C
pH value	:	9.2
concentration	:	200 g/L at 20 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	

Method detail	:	
Result	:	
Remark	:	Other reported values: 49 g/100 mL at 0°C; 55.8 g/100 mL at 100°C (Hazardous Substances Data Bank, online at http://toxnet.nlm.nih.gov,) [Subequently referred to as HSDB, 2002]
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	MSDS as cited in IUCLID (2000)

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** Flash point for propionic acid reported to be 52.3°C (See Appendix I: 2.7)
Reliability	:	
Reference	:	MSDS, Fisher Scientific (2002) from http://www.fishersci.ca/msds/nsf

3.1.1 PHOTODEGRADATION

Type	:	
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) epsilon (max) epsilon (295)
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	1.22 - 1.60 E-12 cm^3/mol/s at 298ºK (measured for free acid)
Remark	:	**Supporting data for dissocation products:** **Acid:** The calculated time to 50% degradation by indirect photolysis of propionic acid was 4.7 years at room temperature and a pH of 9 with a rate constant of 0.47 x 10^9 L/mol.sec (See Appendix I: 3.1.1)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	Atkinson, R., J. Phys. Chem. RefData, Mongraph 1; Meylan, W. and P. Howard, 1993, Atmospheric Oxidation Program Ver. 1.5, Syracuse Research Corp., NY; As cited in IUCLID (2000)

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKb	:	6.76 and 4.75 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Calcium propionate (3445-1), lot number 05322JU, received from Aldrich Chemical Company. White powder, purity of 21.2% calcium
Approximate water solubility	:	Greater than 10,000 mg/L as determined visually in preliminary study

Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of calcium propionate were prepared at a nominal concentration of 0.01 moles/L by dissolving 0.186 grams of test substance in 100 mL of degassed water (ASTM Type II). Each sample was titrated against 0.1 N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 4 incremental additions were made before the first equivalence point and at least 10 incremental additions were made before the second equivalence point. The titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 4 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKb values were 6.76 (SD = 0.0488) and 4.75 (SD= 0.00808) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of proprionic acid, calcium salt, Wildlife International, Ltd. Study No. 534C-120, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	Food
Concentration	:	ca. 2000 mg/l
Substance measured	:	
Method	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Propionic acid, calcium salt is widely used as a mold and rope inhibitor in bread and bakery products at levels approx. 2000 ppm. Also used to prevent mold in certain cheeses and on certain fruit and vegetable products. (IUCLID, 2000). Weighted mean concentration added to baked goods 1100 ppm (FASEB, 1979)
Reliability	:	[1] Reliable without restriction
Reference	:	IUCLID (2000); Federation of American Societies for Experimental Biology (FASEB), Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients, Report of Select Committee on GRAS substances, prepared for US Food and Drug Administration, 1979. PB80104599 [Subequently referred to as FASEB, 1979]

Additional information: According to the Joint FAO/WHO Expert Committee on Food Additives, the estimate of the acceptable daily intakes for man are given as 0 – 10 mg/kg body weight (unconditional acceptance) and 10 – 20 mg/kg body weight (conditional acceptance). This is calculated as the sum of propionic acid, calcium

propionate and sodium propionate. The Expert Commitee stated that there is no reason to believe that propionic acid differs toxicologically from its calcium and sodium salts. (FAO Nutrition Meetings, Report Series No. 40A,B,C, WHO/Food Add./67.29, Toxicological Evaluation of Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases.)

3.3.1 TRANSPORT (Fugacity)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissocation products:** **Acid:** For propionic acid, the Henry's law constant is 4.15 x 10^{-7} atm.m^3/mol at 25°C
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	Aerobic
Guideline/method	:	OECD 302 B
Inoculum	:	Other: activated sludge
Concentration	:	300 mg/L related to DOC (dissolved organic carbon)
Contact time	:	
Degradation	:	100 % after 7 day(s)
Result	:	
Kinetic of test subst.	:	3 hours = 18 % (specify time and % degradation)
Control substance	:	
Kinetic	:	%
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	OECD Guideline 302B, Inherent biodegradability: Modified Zahn-Wellens Test
Method Detail	:	
Result	:	biodegradable
Remark	:	**Supporting data for dissociation products:** **Acid:** Propionic acid is biodegradable in activated sludge, with 40.4% removal of an initial concentration of 500 mg/L after 24 hours and 95% removal of an intial concentration of 400 mg/L after 10 days (See Appendix I: 3.5)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (Ber. V.24.01.89. As cited in IUCLID (2000)

(2000)

3.7 BIOCONCENTRATION

Type	:		
Guideline/method	:		
Species	:		
Exposure period	:	at	°C
Concentration	:		
BCF	:		
Elimination	:		
Year	:		
GLP	:		
Test substance	:		
Method	:		
Method detail	:		
Result	:		
Remark	:		
Reliability	:		
Reference	:		

4.1 ACUTE TOXICITY TO FISH

Type	:	Static
Guideline/method	:	DIN38412 Teil 15, Bestimmung der Wirkkung von Wasserinhaltsstoffen auf Fische
Species	:	*Leuciscus idus*, freshwater fish
Exposure period	:	96 hours
NOEC	:	5000 mg/L
LC0	:	5000 mg/L
LC50	:	> 10000 mg/L
LC100	:	> 10000 mg/L
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1982
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	DIN38412 Teil 15, Bestimmung der Wirkkung von Wasserinhaltsstoffen auf Fische
Method detail	:	
Result	:	Lethality to 2 of 10 fish after 96 hours at 10000 mg/L, no lethality at 5000 mg/L. No toxic symptoms detectable.
Remark	:	For sodium propionate, the 24-h LC50 for *Lepomis macrochirus* was 5000 mg/L. **Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h LC50 for *Cyprinus carpio* was 72 mg/L and the 24-h LC50 for *Lepomis macrochirus* was 188 mg/L. (See Appendix I: 4.1) Reported 96-h LC50 values for propionic acid include 85.3 ppm (95% CI 73.0 – 99.7ppm) for *Lepomis macrochirus* and 67.1 ppm (95% CI: 61.6 – 73.2 ppm) for *Oncorhynchus mykiss*. (US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 10F0958/885187, 08.01.1990. As cited in IUCLID (2000)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Guideline/method	:	Directive 84/449/EEC, C.2, “Acute toxicity for *Daphnia*“
Species	:	*Daphnia magna* (water flea)
Exposure period	:	48 hours
NOEC	:	
EC0	:	250 mg/L
EC50	:	> 500 mg/L
EC100	:	> 500 mg/L
Other	:	24 h EC50 = 250 mg/L
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1989
GLP	:	No
Test substance	:	Calcium dipropionate

Method	:	Directive 84/449/EEC, C.2, “Acute toxicity for *Daphnia*“
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h EC50 for *Daphnia magna* was reported to be 50 mg/L. (See Appendix I: 4.2). Reported 48-h EC50 value for *Daphnia magna* for propionic acid was 22.7 ppm (95% CI: 21.0 – 24.6 ppm) [US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX].
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (1540/88). As cited in IUCLID (2000)

4.3 TOXICITY TO AQUATIC PLANTS (e.g., Algae)

Type	:	Growth inhibition
Guideline/method	:	OECD guideline 201, Algae, Growth Inhibition Test
Species	:	*Scenedesmus subspicatus* (freshwater green algae)
Endpoint	:	
Exposure period	:	72 hours
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	> 500 mg/L
EC20	:	> 500 mg/L
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	No
Year	:	1988
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	OECD guideline 201, Algae, Growth Inhibition Test
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** For propionic acid, the 72-h EC50 for *Scenedesmus subspicatus* was reported to be 43 - 45.8 mg/L (See Appendix I: 4.3)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Labor Oekologie, unveroeffentlichte Untersuchung,(Laboratory of Ecology, unpublished research) (1540/88). As cited in IUCLID (2000)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo :
Type :
Guideline/method :
Species :
Number of animals :
Males :
Females :
Doses :
Males :
Females :
Vehicle :
Route of administration :
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behavior :
Deg. product :
Deg products CAS#
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Propionic acid is a normal intermediary metabolite in animals and humans. Propionic acid occurs naturally in various foods including butter and cheese. (FASEB, 1979).
Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Guideline/method :
Species : Rat
Strain :
Sex : Male and female
Number of animals :
Vehicle :
Doses :
LD50 : 3920 – 4380 mg/kg bw.
Year :
GLP :
Test substance : Calcium dipropionate
Method :
Method detail :
Result : LD50 was 3920 – 4380 mg/kg bw. For male rats, LD50 was 4280 or 4380

		mg/kg. For female rats, LD50 was 3920 or 4040 mg/kg
Remark	:	For sodium propionate, the LD50 for the rat was 5100 mg/kg. **Supporting data for dissociation products:** **Acid:** For propionic acid, the following LC50 values for rats have been reported: 3470 mg/kg; 4290 mg/kg; 2600 mg/kg. For sodium propionate, the LD50 for the rat was 5100 mg/kg. (See Appendix I: 5.1.1)
Reliability	:	[4] Not assignable. Text is in Japanese, only tables appear in English
Reference	:	Kobayashi, H., H. Ichikawa, N. Kamiya, S. Yoshida, and K. Hiraga (1976). The results on acute toxicities of food additives. Ann. Rep. Tokyo Metr. Res. Lab. P.H., 27-2, 159-160. Also cited and interpreted in IUCLID (2000)
Additional references	:	Other oral LD50 values for rats: 5160 mg/kg bw; 2600 mg/kg bw; 6400 mg/kg bw (As cited in IUCLID, 2000)

Type	:	LD50
Guideline/method	:	
Species	:	Mouse
Strain	:	
Sex	:	Male and female
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	2350 - 2900 mg/kg bw.
Year	:	
GLP	:	
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	
Result	:	LD50 was 2350 - 2900 mg/kg bw. For male mice, LD50 was 2350 or 2600 mg/kg. For female mice, LD50 was 2400 or 2900 mg/kg
Remark	:	For a similar compound, sodium propionate, the LD50 for the mouse was 5100 mg/kg bw, as cited in FASEB Report: Evaluation of the health aspects of propionic acid..., prepared for FDA, 1979.
Reliability	:	[4] Not assignable. Text is in Japanese, only tables appear in English
Reference	:	Kobayashi, H., H. Ichikawa, N. Kamiya, S. Yoshida, and K. Hiraga (1976). The results on acute toxicities of food additives. Ann. Rep. Tokyo Metr. Res. Lab. P.H., 27-2, 159-160. Also cited and interpreted in IUCLID (2000)
Additional references		LD50 of 3340 mg/kg for DD-strain mice is cited in FASEB (1979)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	Limit test
Guideline/method	:	
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	4 hours
LC50	:	> 5.4 mg/L
Year	:	
GLP	:	No
Test substance	:	
Method	:	
Method detail	:	

Result	:	The LC50 was reported to be > 5.4 mg/L
Remark	:	Also tested sodium propionate, dust aerosol, with same result. **Supporting data for dissocation products:** **Acid:** Under similar conditions as reported above for calcium propionate and sodium propionate, the LC50 for propionic acid was >4.9 mg/L. (See Appendix I: 5.1.2)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 78/29, 19.12.1980. As cited in IUCLID (2000)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	500 mg/kg bw
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	The LD50 was reported as 500 mg/kg bw
Remark	:	No further information. Same result cited for propionic acid
Reliability	:	[4] Not assignable. Only secondary literature.
Reference	:	Patty Ind. Hyg. Toxicol. (1982); Smyth, H.F. et al., Am. Ind. Hyg. Assoc. J. 23:95-107 (1962); Union Carbide Datasheet. As cited in IUCLID (2000)

5.2.1 SKIN IRRITATION

Type	:	Skin irritation
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	1973
GLP	:	No
Test substance	:	Calcium propionate feed grade, sodium propionate
Method	:	Draize test
Method detail	:	
Result	:	Not irritating
Remark	:	Sodium propionate was found to be not irritating in the Draize skin irritation test with rabbits. (See Appendix 1: 5.2.2) **Supporting data for dissociation products:**

		Acid: Propionic acid caused mild irritation to rabbits following 4 h closed contact of the skin with a 2.5% aqueous solution, mild to moderate irritation with 25% solution, and moderate to severe irritation and corrosion at concentrations of 40% and above. Propionic acid ws a severe irritant to guinea pig skin. (See Appendix I: 5.2.1)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 78/28, 78/29 and 78/30. 25.04.1979. As cited in IUCLID (2000)

5.2.2 EYE IRRITATION

Type	:	Eye irritation
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Method	:	
Year	:	1973
GLP	:	
Test substance	:	Calcium propionate feed grade, sodium propionate
Method	:	Draize test
Method detail	:	
Result	:	Not irritating
Remark	:	Sodium propionate was found to be not irritating in the Draize eye irritation test with rabbits. Propionic acid was irritating to rabbits (See Appendix 1: 5.2.2)
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	BASF AG, Dept. Toxicology, unpublished study 78/28, 78/29 and 78/30. 25.04.1979. As cited in IUCLID (2000)

5.4 REPEATED DOSE TOXICITY

Type	:	Repeated dose
Guideline/method	:	
Species	:	Rat
Strain	:	Wistar Han/BGA
Sex	:	Male and female
Number of animals	:	40
Route of admin.	:	Oral feed
Exposure period	:	90 days
Frequency of treatment	:	Daily
Post exposure period	:	One group for control and two highest doses over 90 and 180 days
Doses	:	0.2, 0.5, 1 and 4% (= 166, 415, 830, 3320 mg/kg bw)
Control group	:	Yes
NOAEL	:	0.2% (166 mg/kg) for males, 1% (830 mg/kg) for females
LOAEL	:	
Other	:	

Year	:	
GLP	:	
Test substance	:	Not clarified but presumed to be calcium propionate
Method	:	
Method detail	:	
Result	:	No abnormalities in clinical and hematological examination and organ weights. In forestomach of males, hyperkeratosis and hyperplasia of mucosa, at 4% 1/10 atypical basal cell proliferation and 5/10 dysplasia. In forestomach of females, hyperkeratosis and hyperplasia at 4% (hyperkeratosis also in controls) in different regions of forestomach. Effects largely reversible during 90-day post exposure observation period. After 180 days appearance of first age-related changes in the forestomach.
Remark	:	Forty female Wistar rats fed sodium propionate at 20000 ppm (1320 mg/kg) for one year did not exhibit any hematological, clinicochemical, or urinalytic changes. There were no changes in organ weights and the body weight at the end of the study was 290 g versus 299 g in controls. [Imai, S. , S. Sekigawa, J. Morimoto, Y. Ohno, H. Yamamoto, T. Okuyama, K. Nakamor and Y. Tsubura (1981). Additive toxicity of sodium propionate and/or sorbic acid in SLC-Wistar rats for one year. J. Nara. Med. Ass. 32:715-722. Also interpreted and cited in IUCLID (2000)]. **Supporting data for dissociation products:** **Acid:** Beagles fed propionic acid for 90 days exhibited lack of appetite at the highest dose (2000 mg/kg bw) but no other clinical, hematological or clinico-chemical effects. (See Appendix I: 5.4). Propionic acid in the diet (4% or 3320 mg/kg) of rats caused enhanced incorporation of methyl-H3-thymidine in the mucosa of the forestomach after 21 and 28 days of treatment, and macroscopic and histological lesions (general and nodular mucosal thickening) were observed in the forestomach after 27 days. This may reflect the response of the forestomach epithelium to changed pH (Rodrigues, C., Lok, E., Nera, E., Iverson, F., Page, D., Karpinski, K. and Clayson, D.B., 1986. Short-term effects of various phenols and acids on the Fischer 344 male rat forestomach epithelium, Toxicology 38:103-117).
Reliability	:	[4] Not assignable. Only secondary literature
Reference	:	Altman H-J and Grunow, W., „Ergeb. Neuer. Fuetterungsvers.m.Propions.u.i.Salzen“ unpubl. Report Fed. Health Agency (BGA Berlin ,'88). As cited in IUCLID (2000)

Addtional References for Repeated Dose Toxicity: Rats (Wistar HAN/BGA) were exposed to 40,000 ppm (3320 mg/kg) calcium propionate in the diet for 4 weeks (females) or 8 weeks (males). Feed consumption, body weight gain and absolute organ weights were reduced. For the 4-week exposure, a slight thickening of the limiting ridge in the forestomach was observed. Hyperkeratosis and hyperplasia of mucosa were clearly far less pronounced for calcium propionate as compared to the acid [Altman H.-J. and Grunow, W., Arbietspapier zur Tox. V. Propions. U.i. Ca-, K-, und Na-Saltze, unpubl. Report Fed Health Agency, BGA Berlin ,88 and Altman, H.-J. and Grunow, W., Ergeb. Neuer. Fuetterungsvers.m. Propions.u.i.Salzen“ unpubl. Report Fed. Health Agency (BGA Berlin ,'88). As cited in IUCLID (2000)]. In a paired feeding study, rats given calcium propionate or sodium propionate (approximately 750 mg/kg/day, expressed as propionic acid, for 4 weeks followed by 1200 mg/kg/day for 3 weeks) did not show any difference in weight gain from control animals. No hematological or clinicochemical parameters were measured in this study [Harshbarger, K.E., 1942. Report of a study on the toxicity of several food preserving agents. J. Dairy Sci. 25:169-174. Also cited and interpreted in FASEB (1979).] In a 90-day feeding study with male beagles, 435000 ppm calcium propionate caused diarrhea and vomiting in all animals but 14500 ppm caused these effects in only one dog. No hematological or clinicochemical parameters were measured in this study. [Altman H-J and Grunow, W., „Ergeb. Neuer. Fuetterungsvers.m.Propions.u.i.Salzen“ unpubl. Report Fed. Health Agency (BGA Berlin ,'88); BASF AG, Dept. Toxicology, unpublished study 31D0449/87039, 06.04.1989. As cited in IUCLID (2000)].

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Repair test (rec assay) and reversion assay
Species	:	*Bacillus subtilis* (rec assay); *Escherichia coli* and *Salmonella typhimurium* (reversion assay)
Strain	:	*B. subtilis*: H17 Rec^+ and M45Rec^-; *E.coli*: WP2 *hcr trp*; *S. typhimurium*: TA98, TA100, TA1535, TA 1537, TA1538
Test concentrations	:	No data specified
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. Activation system consisted of S-9 mix prepared from liver homogenate of Arochlor 1254-pretreated male rats (i.p at 500 mg/kg)
Year	:	
GLP	:	No data
Test substance	:	Calcium propionate; purity > 98%
Method	:	Rec assay using paper disk method, according to Shirasu, Y. et al., Mutat. Res. 56: 121-129. Reverse mutation assay according to Ames, B.N., Mutat. Res. 31: 347-364
Method detail	:	DMSO solvent.
Result	:	Negative
Remark	:	Sodium propionate was negative in the Ames assay. (Ishidate, et al., 1984, as cited in Basler et al., 1987) **Supporting information for dissociation products:** **Acid:** Propionic acid was evaluated for genotoxic properties using the *E.coli* DNA repair assay, the SOS chromotest, the Salmonella/microsome mutagenicity test, the sister chromatid exchange test *in vitro* and the micronucleus test *in vivo*. All tests except the DNA repair assay yielded negative results. The authors concluded that this evidence supported other evidence, including studies with calcium and sodium propionate, that propionic acid was not mutagenic (Basler, A., von der Hude, W. and Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290). The authors conclude that since calcium and sodium propionate dissociate in aqueous solution and react with a proton to form the acid, results with all three test substances can be compared.
Reliability	:	[2] Reliable with restrictions. Conducted according to scientifically acceptable methods.
Reference	:	Ohta, T., M. Moriya, Y. Kaneda, K. Watanabe, T. Miyazawa, F. Sugiyama and Y. Shirasu (1980). Mutagenicity screening of feed additives in the microbial system. Mutat. Res. 77: 21-30. Also cited in IUCLID (2000)

Addtional References for Genetic Toxicity in Vitro: In the Ames test with *S. typhimurium* (TA98, TA100, TA 1535, TA1537 and TA 1538), with a test concentration of 0.95 mg/mL calcium propionate, with and without metabolic activation (S9 from rat, mouse and hamster), the result was negative. [Altman H.-J. and Grunow, W., Arbietspapier zur Tox. V. Propions. U.i. Ca-, K-, und Na-Saltze, unpubl. Report Fed Health Agency, BGA Berlin ,88; Litton Bionetics report prepared for FDA, PB 266897 (1976). As cited in IUCLID (2000).] Negative results were obtained in the Ames test with *Salmonella typhimurium* strains TA-1535, TA-1537, TA-1538 and *Saccaromyces cerevisiae* strain D-4, with activation (preparations were from lung, liver, and testis of mouse, rat, and monkey. [Litton Bionetics, Inc., 1974. Mutagenic evaluation of compound FDA 71-36, calcium propionate, NTIS PB245448]. Calcium dipropionate was negative in the cytogenetic assay using CHL cells, without activation, and in the sister chromatid exchange assay,using V79 cells, with and without activation [Altman, ibid.]. Calcium and sodium propionate were negative in the Ames test; calcium propionate caused a slight

increase in the number of Chinese hamster lung cells but sodium propionate caused no chromosomal abberrations even at a higher concentration (Ishidate et al., 1984, as cited in Basler et al., 1987).

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Cytogenetic assay and dominant lethal assay
Guideline/method	:	
Species	:	Rat
Strain	:	Sprague-Dawley CD
Sex	:	male
Route of admin.	:	Oral (gastric intubation)
Exposure period	:	Acute study: single dose, then observed for 10 days. Subacute study: Dosed every 24 hours for 5 days.
Doses	:	5000 mg/kg (single dose) or 50, 500 and 5000 mg/kg (subacute)
Year	:	1973
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	Negative control (saline) and postive control used. Single dose study conducted with two rats at 5000 mg/kg bw, then repeated with ten rats at same dose.
Result	:	No increase of chromosome aberrations in bone marrow cells. In addition, no dominant lethal mutations detected.
Remark	:	No increase in chromosome abberations in the bone marrow cells of the rat were observed after dosing with sodium propionate (See Appendix I: 5.6) **Supporting data for dissociation products:** **Acid:** Propionic acid was not genotoxic in the micronucleus test *in vivo*. (Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).
Reliability	:	[1] Reliable without restrictions. Methods described and complete data presented. Comparable to guideline study.
Reference	:	Litton Bionetics, Inc. (1974). Mutagenic evaluation of compound FDA 71-36. Report prepared for FDA, NTIS PB 245448 (1974).

Type	:	Host mediated assay
Guideline/method		
Species	:	Mouse
Strain	:	ICR
Sex	:	Male
Route of admin.	:	Oral (gastric intubation)
Exposure period	:	Acute study: single dose, then observed for 10 days. Subacute study: Dosed every 24 hours for 5 days.
Doses	:	5000 mg/kg (single dose) or 50, 500 and 5000 mg/kg (subacute)
Year	:	1973
GLP	:	No
Test substance	:	Calcium dipropionate
Method	:	
Method detail	:	Negative control (saline) and positive controls used. Ten animals at each dose level for both acute and subacute study.
Result	:	Increase in reversion frequency of *S. typhimurium* G-46 but not dose-related. No mutations in strain TA-1530 and *Saccharomyces cerevisiae* D3. A single dose was marginally recombinogenic in the acute trials using *S. cerevisiae* D3 but none of the other acute or subacute doses showed this effect.

Remark	:	
Reliability	:	[1] Reliable without restrictions. Methods described and complete data presented. Comparable to guideline study.
Reference	:	Litton Bionetics, Inc. (1974). Mutagenic evaluation of compound FDA 71-36. Report prepared for FDA, NTIS PB 245448 (1974).

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Mouse
Strain	:	Albino CD-1
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 17 of gestation
Doses	:	3, 14, 65, 300 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	1972
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 25-30 mice were used. Negative controls were intubated with water, positive controls were administered 150 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,11,15 and 17 of gestation. On day 17 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the soft or skeletal tissues in treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.

Type	:	Developmental toxicity

Guideline/method	:	
Species	:	Rabbit
Strain	:	Dutch-belted
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -18 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 29 of gestation
Doses	:	4, 19, 86, 400 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 15-25 rabbits were used. Negative controls were intubated with water, positive controls were administered 2.5 mg/kg of 6-aminonicotinamide on day 9. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,12,18 and 29 of gestation. On day 29 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, mplantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. Live fetuses were placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed and examined for visceral abnormalities (by dissection), then cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.

Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Hamster
Strain	:	Golden hamsters from an outbred strain (no further data)
Sex	:	Female
Route of admin.	:	Gavage
Exposure period	:	Day 6 -10 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 14 of gestation

Doses	:	4, 19, 86, 400 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (400 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate
Method	:	
Method detail	:	Groups of 22 golden hamsters were used. Negative controls were intubated with water, positive controls were administered 250 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,8,10, and 14 of gestation. On day 14 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effects on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.

Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Rat
Strain	:	Albino, Wistar
Sex	:	Female
Route of admin.	:	Oral intubation
Exposure period	:	Day 6 -15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Until day 20 of gestation
Doses	:	3, 14, 65, 300 mg/kg/d
Control group	:	Yes, concurrent sham-treated
NOAEL maternal tox.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
NOAEL teratogen.	:	NOAEL not reported, but no effects seen at highest dose (300 mg/kg/d)
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	No
Test substance	:	Calcium propionate

Method	:	
Method detail	:	Groups of 24 rats were used. Negative controls were intubated with water, positive controls were administered 250 mg/kg/d of aspirin. Animals were observed daily for appearance, behavior, food and water consumption. Body weight was recorded on days 0,6,11,15 and 20 of gestation. On day 20 of gestation, all dams were subjected to Casarean section and the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. Body weights of live pups recorded and urogenital tract of each dam was examined for anatomical normality. All fetuses were examined grossly for abnormalities. One third of the fetuses of each litter underwent detailed visceral examination under 10x magnification; two thirds cleared, stained and examined for skeletal defects.
Result	:	No clearly substance-related effect on pregnancy parameters or on maternal or fetal survival were observed. The number of abnormalities in the treated groups was not different from negative controls.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Generally comparable to current guideline methodology, but level of recorded detail (both methods and results) is not consistent with current guidelines. No statistical analyses of results was performed.
Reference	:	Food and Drug Research Labs, Inc.,(1972) Teratologic Evaluation of FDA 71-36 (Calcium propionate) in mice, rats, hamsters and rabbits, Final report for FDA, NTIS PB-221778.
Type	:	Developmental toxicity
Guideline/method	:	
Species	:	Chicken
Strain	:	
Sex	:	
Route of admin.	:	Injection into air cell or yolk sac of eggs
Exposure period	:	Preincubation or at 96 hours
Frequency of treatment	:	
Duration of test	:	
Doses	:	5, 10, 100 mg/kg of egg
Control group	:	Yes, concurrent vehicle
NOAEL maternal tox.	:	
NOAEL teratogen.	:	100 mg/kg
Other	:	High mortality rates at doses of 5 and 10 mg/kg
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	Calcium propionate
Method	:	
Method detail	:	
Result	:	Not teratogenic to developing chicken embryo at levels up to 100 mg/kg of egg preincubation or at 96 h via the yolk and air cell. A dose of 10 mg/kg of egg produced high mortality rates compared to solvent controls, and a dose of 5 mg/kg administered preincubation via the yolk caused a high mortality rate.
Remark	:	
Reliability	:	[4] Not assignable. Only secondary reference.
Reference	:	Mississippi State University, 1973. Investigation of the toxic effects of GRAS substances to the developing chicken embryo: calcium propionate. As cited in FASEB (1979)

As cited in FASEB (1979)

5.8.3 TOXICITY TO REPRODUCTION

Type	:
Guideline/method	:
In vitro/in vivo	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatm.	:
Duration of test	:
Doses	:
Control group	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

7.0 OTHER INFORMATION

7.1 CARCINOGENICITY

Supporting information for dissociation products:
Acid: Pre-neoplastic/pre-cancerous changes in rats fed 4% (2640 mg/kg) propionic acid were reported by Griem (1985). Hyperplasia, hyperplastic ulcers, papillomas and proliferation of the basal cells in the mucuosa of the forestomach were observed. Over the lifetime exposure, the high dose (4% propionic acid) resulted in 19/20 rats with dysplasia of glandular stomach mucosa while this effect was seen in 10/20 rats at the low dose (0.4%) and 5/20 control rats. However, Basler et al. (1987) concluded that propionic acid is not mutagenic and that genotoxic events are unlikely to be involved in the generation of these forestomach lesions. (See Appendix I: 5.7; also Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).

Note: Appendix I refers to the IUCLID profile for Propionic Acid

1.0 SUBSTANCE INFORMATION

Generic Name	:	Propionic acid, cobalt salt
Chemical Name	:	Propionic acid, cobalt salt
CAS Registry No.	:	1560-69-6
Component Cas Nos.	:	
EINECS No.	:	
Structural Formula	:	$C_6H_{10}O_4Co$
Molecular Weight	:	205.1
Synonyms and Tradenames	:	Cobalt propionate
Reference	:	MSDS dated 3/27/02 prepared by OMG Americas, Inc.

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Melting point for propionic acid is reported to be 22.4°C (See Appendix I: 2.1)
Result	:	
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	°C at hPa
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Boiling point for propionic acid is reported to be 140.7 – 141.6°C (See Appendix I: 2.2)
Reliability	:	
Reference	:	

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Density for propionic acid is reported to be 0.992 g/cm^3 at 20°C (See Appendix I: 2.3)

Reliability :
Reference :

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value : hPa at °C
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Vapor pressure for propionic acid reported to be 5 hPa at 20°C (See Appendix I: 2.4)
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Log Pow for propionic acid reported to be 0.25 – 0.33 (See Appendix I: 2.5)
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method
Value :
pH value :
concentration :
Temperature effects :
Examine different pol. :
pKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :

Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.7 FLASH POINT

Type :
Guideline/method :
Value : °C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Flash point for propionic acid reported to be 52.3°C (See Appendix I: 2.7)
Reliability :
Reference :

3.1.1 PHOTODEGRADATION

Type	:	
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) epsilon (max) epsilon (295)
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The calculated time to 50% degradation by indirect photolysis of propionic acid was 4.7 years at room temperature and a pH of 9 with a rate constant of 0.47 x 10^9 L/mol.sec (See Appendix I: 3.1.1)
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKb	:	7.58 and 4.85 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Cobalt propionate, received from OMG Americas, Inc. Purple powder, purity not reported.
Approximate water solubility	:	5000 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Six replicate samples of cobalt propionate were prepared at a nominal concentration of 0.01 moles/L by dissolving 0.259

grams of test substance in 100 mL of degassed water (ASTM Type II). Each sample was titrated against 0.1 N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.

Result : Mean (N = 3) pKb values were 7.58 (SD = 0.0290) and 4.85 (SD= 0.0420) at 20°C

Remark : The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F. And W.B. Nixon, 2002. Determination of the dissocation constant of proprionic acid, cobalt (2+) salt, Wildlife International Ltd., Study No. 534C-122, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement :

Media :

Concentration :

Substance measured :

Method :

Method :

Method detail :

Result :

Remark : **Supporting data for dissociation products:**
Acid: Propionic acid, calcium salt is widely used as a mold and rope inhibitor in bread and bakery products at levels approx. 2000 ppm. Also used to prevent mold in certain cheeses and on certain fruit and vegetable products. (IUCLID, 2000). Weighted mean concentration added to baked goods 1100 ppm (FASEB, 1979)

Reliability :

Reference : IUCLID (2000); Federation of American Societies for Experimental Biology (FASEB), Evaluation of the health aspects of propionic acid, calcium propionate, sodium propionate, dilauryl thiodipropionate, and thiodipropionic acid as food ingredients, Report of Select Committee on GRAS substances, prepared for US Food and Drug Administration, 1979. PB80104599 [Subequently referred to as FASEB, 1979]

Additional information: According to the Joint FAO/WHO Expert Committee on Food Additives, the estimate of the acceptable daily intakes for man are given as 0 – 10 mg/kg body weight (unconditional acceptance) and 10 – 20 mg/kg body weight (conditional acceptance). This is calculated as the sum of propionic acid, calcium propionate and sodium propionate. The Expert Commitee stated that there is no reason to believe that propionic acid differs toxicologically from its calcium and sodium salts. (FAO Nutrition Meetings, Report Series No. 40A,B,C, WHO/Food Add./67.29, Toxicological Evaluation of Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases.)

3.3.1 TRANSPORT (Fugacity)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** For propionic acid, the Henry's law constant is 4.15 x 10^{-7} atm.m^3/mol at 25°C
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	
Contact time	:	
Degradation	:	
Result	:	
Kinetic of test subst.	:	
Control substance	:	
Kinetic	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method Detail	:	
Result	:	
Remark	:	In the Modified Zahn-Wellens inherent biodegradability test, calcium propionate was found to be biodegradable (100% after 7 days). (See Appendix I: 3.5) **Supporting data for dissociation products:** **Acid:** Propionic acid is biodegradable in activated sludge, with 40.4% removal of an initial concentration of 500 mg/L after 24 hours and 95% removal of an intial concentration of 400 mg/L after 10 days (See Appendix I: 3.5) **Metal:** NA
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:		
Guideline/method	:		
Species	:		
Exposure period	:	at	°C
Concentration	:		
BCF	:		
Elimination	:		
Year	:		
GLP	:		
Test substance	:		
Method	:		
Method detail	:		
Result	:		
Remark	:		
Reliability	:		
Reference	:		

4.2 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	For calcium dipropionate, the 96-h LC50 for the freshwater fish *Leuciscus idus* was reported to be >10,000 mg/L. For sodium propionate, the 24-h LC50 for *Lepomis macrochirus* was 5000 mg/L. **Supporting data for dissociation products:** **Acid:** For propionic acid, the 48-h LC50 for *Cyprinus carpio* was 72 mg/L and the 24-h LC50 for *Lepomis macrochirus* was 188 mg/L. (See Appendix I: 4.1) Reported 96-h LC50 values for propionic acid include 85.3 ppm (95% CI 73.0 – 99.7ppm) for *Lepomis macrochirus* and 67.1 ppm (95% CI: 61.6 – 73.2 ppm) for *Oncorhynchus mykiss*. (US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX). **Metal:** For cobalt chloride, the 96-h LC50 was 333 mg Co/L for *Cyprinus carpio* and 1,406 mg Co/L for *Onchorynchus mykiss* (ECOTOX data base).
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	

Method detail :
Result :
Remark : For calcium dipropionate, the 48-h EC50 for *Daphnia magna* was reported to be > 500 mg/L.
Supporting data for dissociation products:
Acid: For propionic acid, the 48-h EC50 for *Daphnia magna* was reported to be 50 mg/L. (See Appendix I: 4.2). Reported 48-h EC50 value for *Daphnia magna* for propionic acid was 22.7 ppm (95% CI: 21.0 – 24.6 ppm) [US EPA Office of Pesticide Programs Environmental Effects Database, cited in ECOTOX].
Metal: For cobalt chloride, the reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base).
Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (e.g., Algae)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
EC20 :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : For calcium dipropionate, the 72-h EC50 for *Scenedesumus subspicatus* was reported to be > 500 mg/L.
Supporting data for dissociation products:
Acid: For propionic acid, the 72-h EC50 for *Scenedesmus subspicatus* was reported to be 43 - 45.8 mg/L (See Appendix I: 4.3).
Metal: For cobalt chloride, the 96-h EC50 for *Chlorella vulgaris* was 0.522 mg/L (ECOTOX data base).
Reliability :
Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo :
Type :
Guideline/method :
Species :
Number of animals :
Males :
Females :
Doses :
Males :
Females :
Vehicle :
Route of administration :
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behavior :
Deg. product :
Deg products CAS#
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Propionic acid is a normal intermediary metabolite in animals and humans. Propionic acid occurs naturally in various foods including butter and cheese. (FASEB, 1979).
Metal: Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. *Clin. Tox.* 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Year	:	
LD50	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	For calcium dipropionate, oral LD50 values for the rat were 3920 – 4380 mg/kg and for the mouse were 2350 – 2900 mg/kg. For sodium propionate, the oral LD50 for the mouse was 5100 mg/kg. (See Appendix I: 5.1.1). **Supporting data for dissociation products:** **Acid:** For propionic acid, the following LC50 values for rats have been reported: 3470 mg/kg; 4290 mg/kg; 2600 mg/kg. (See Appendix I: 5.1.1). **Metal:** Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg $CoCl_2$/kg bw (equivalent to 19.1 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 55.4 to 72.5 mg Co/kg bw) (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 55.4 mg/kg bw when expressed as cobalt (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	
Additional references	:	

5.1.3 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
Year	:	
GLP	:	
LC50	:	
Test substance	:	
Method	:	
Method detail	:	

Result :

Remark : For calcium propionate and sodium propionate, the LC50 for inhalation of aerosol dust was reported to be > 5.4 mg/L. (See Appendix I: 5.1.2)
Supporting data for dissociation products:
Acid: Under similar conditions as reported above for calcium propionate and sodium propionate, the LC50 for propionic acid was >4.9 mg/L. (See Appendix I: 5.1.2).
Metal: The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m^3 as mixed cobalt oxides. (ATSDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was >10 mg/L (IUCLID, 2000).

Reliability :

Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :

Guideline/method :

Species :

Strain :

Sex :

Number of animals :

Vehicle :

Doses :

LD50 :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark : For calcium propionate, the LD50 for dermal exposure for the rabbit was reported to be 500 mg/kg.
Supporting data for dissociation products:
Acid: For propionic acid, the LD50 for dermal exposure for the rabbit was reported to be 500 mg/kg (See Appendix I: 5.1.3).
Metal: Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).

Reliability :

Reference :

5.2.1 SKIN IRRITATION

Type :

Guideline/method :

Species :

Strain :

Sex :

Concentration :

Exposure :

Exposure time :

Number of animals :

Vehicle :

Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Calcium priopionate and sodium propionate were found not irritating in the Draize skin irritation test with rabbits. (See Appendix I: 5.2.1).
Supporting data for dissociation products:
Acid: Propionic acid caused mild irritation to rabbits following 4 h closed contact of the skin with a 2.5% aqueous solution, mild to moderate irritation with 25% solution, and moderate to severe irritation and corrosion at concentrations of 40% and above. Propionic acid was a severe irritant to guinea pig skin. (See Appendix I: 5.2.1).
Metal: Cobalt is reported to be irritating to the skin (IUCLID, 2000).
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Method :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Calcium propionate and sodium propionate were found not irritating in the Draize eye irritation test with rabbits. Propionic acid was irritating to rabbits (See Appendix I: 5.2.2)
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :

Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Calcium propionate and sodium propionate, administered in feed over 7 weeks at 750 – 1200 mg/kg/day, did not affect weight gain in rats. In a 90-day feeding study, the NOAEL for calcium propionate was 166 mg/kg for male rats and 830 mg/kg for female rats. For a one-year exposure period, the oral NOAEL for sodium propionate in rats was 1320 mg/kg.
Supporting information for dissociation products:
Acid: Beagles fed propionic acid for 90 days exhibited lack of appetite at the highest dose (2000 mg/kg bw) but no other clinical, hematological or clinico-chemical effects. (See Appendix I: 5.4). Propionic acid in the diet (4% or 3320 mg/kg) of rats caused enhanced incorporation of methyl-H3-thymidine in the mucosa of the forestomach after 21 and 28 days of treatment, and macroscopic and histological lesions (general and nodular mucosal thickening) were observed in the forestomach after 27 days. This may reflect the response of the forestomach epithelium to changed pH (Rodrigues, C., Lok, E., Nera, E., Iverson, F., Page, D., Karpinski, K. and Clayson, D.B., 1986. Short-term effects of various phenols and acids on the Fischer 344 male rat forestomach epithelium, Toxicology 38:103-117).
Metal: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :
Cytotoxic concentr. :

Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Calcium propionate was not mutagenic in a variety of assays. Calcium and sodium propionate were negative in the Ames test; calcium propionate caused a slight increase in the number of Chinese hamster lung cells but sodium propionate caused no chromosomal abberrations even at a higher concentration [Ishidate et al., 1984, as cited in Basler et al., 1987].
Supporting information for dissociation products:
Acid: Propionic acid was evaluated for genotoxic properties using the *E.coli* DNA repair assay, the SOS chromotest, the Salmonella/microsome mutagenicity test, the sister chromatid exchange test *in vitro* and the micronucleus test *in vivo*. All tests except the DNA repair assay yielded negative results. (Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).
Metal: Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be generally non-mutagenic in bacterial assays, but increased frequency of genetic conversions have been reported in yeast. Cobalt compounds with a valence state of III were weakly mutagenic in bacterial systems (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : Calcium dipropionate was not mutagenic in the cytogenetic assay and dominant lethal assay with rats, nor in the host-mediated assay with mice. No increase in chromosome abberations in the bone marrow cells of the rat were observed after dosing with sodium propionate (See Appendix I: 5.6).
Supporting information for dissociation products:
Acid: Propionic acid was not gentoxic in the micronucleus test *in vivo*. (Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).
Metal: Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt

mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells. Increased micronucleus formation was observed following *i.p.* injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (as cobalt chloride) (NOEL) (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : In developmental toxicity tests with various species, no maternal or teratogenic effects of calcium propionate were seen at the highest dose used, e.g. 300 mg/kg/day for mice and rats; 400 mg/kg/day for rabbits and golden hamsters.

Supporting information for dissociation products:

Metal: In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :

Guideline/method	:	
In vitro/in vivo	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatm.	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

8.0 OTHER INFORMATION

8.1 CARCINOGENICITY.

Supporting information for dissociation products:
Acid: Pre-neoplastic/pre-cancerous changes in rats fed 4% (2640 mg/kg) propionic acid were reported by Griem (1985). Hyperplasia, hyperplastic ulcers, papillomas and proliferation of the basal cells in the mucuosa of the forestomach were observed. Over the lifetime exposure, the high dose (4% propionic acid) resulted in 19/20 rats with dysplasia of glandular stomach mucosa while this effect was seen in 10/20 rats at the low dose (0.4%) and 5/20 control rats. However, Basler et al. (1987) concluded that propionic acid is not mutagenic and that genotoxic events are unlikely to be involved in the generation of these forestomach lesions. (See Appendix I: 5.7; also Basler, A., von der Hude, W. And Scheutwinkel, M., 1987. Screening of the food additive propionic acid for genotoxic properties, Fd. Chem. Toxic. 25:287-290).
Metal: The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). “No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt.” (ATSDR Sept 2001 Draft).

Note: Appendix I is Robust Summaries and SIDS Dossier for 2-ethylhexanoic acid.

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, potassium salt
Chemical Name	:	Hexanoic acid, 2-ethyl, potassium salt
CAS Registry No.	:	3164-85-0
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$C_8H_{17}KO_3$
Molecular Weight	:	200.3105
Synonyms and Trade names	:	Potassium 2-ethylhexanoate hydrate; potassium 2-ethyl hexanoate;
References	:	http://www.chemfinder.com

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Melting point is reported as –118.4°C for 2-ethylhexanoic acid (See Appendix I: 3.1)
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	> 350 °F
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Mixture of potassium 2-ethylhexanoate (80% max. by weight) and diethylene glycol (30% max. by weight)
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (See Appendix I.: 3.2)
Reliability	:	
Reference	:	MSDS dated 4/10/00, prepared by the Shepherd Chemical Company

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	1.11
Year	:	
GLP	:	
Test substance	:	Mixture of potassium 2-ethylhexanoate (80% max. by weight) and diethylene glycol (30% max. by weight)
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference		MSDS dated 4/10/00, prepared by the Shepherd Chemical Company

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Vapor pressure is reported as 1.33 x 10^{-3} kPa at 20°C for 2-ethylhexanoic acid (See Appendix I: 3.3)
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (See Appendix I: 3.4).
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	Negligible
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	Mixture of potassium 2-ethylhexanoate (80% max. by weight) and diethylene glycol (30% max. by weight)
Deg. products CAS#	:	
Method	:	
Method detail	:	

Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The water solubility of 2-ethylhexanoic acid was reported to be 25 mg/L at 25°C (See Appendix I: 3.5).
Reliability	:	
Reference	:	MSDS dated 4/10/00, prepared by the Shepherd Chemical Company

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	> 242 °F
Year	:	
GLP	:	
Test substance	:	Mixture of potassium 2-ethylhexanoate (80% max. by weight) and diethylene glycol (30% max. by weight)
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** A flashpoint of 118°C was reported for 2-ethylhexanoic acid (See Appendix I: 3.6).
Reliability	:	
Reference	:	MSDS dated 4/10/00, prepared by the Shepherd Chemical Company

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKb	:	6.89 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Potassium 2-ethylhexanoate, lot number D14H36, received from Alfa Aesar Chemical Company. Colorless crystal, purity of 95.3%.
Approximate water solubility	:	Greater than 10 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of potassium 2-ethylhexanoate were prepared at a nominal concentration of 0.01 moles/L by dissolving 0.18 grams of test substance in degassed water (ASTM Type II). Each sample was titrated against 0.1N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 8 incremental additions were made before the equivalence point and the titration was carried past the

equivalence point. Values of pK were calculated for a minimum of 8 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.

Result : Mean (N = 3) pKb value was 6.89 (SD = 0.0045) at 20°C

Remark : The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of potassium 2-ethylhexanoate, Wildlife International, Ltd. Study No. 534C-103, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :

Kinetic of test subst.	:	%	(specify time and % degradation)
		%	
		%	
		%	
		%	
Control substance	:		
Kinetic	:	%	
		%	
Deg. product	:		
Year	:		
GLP	:		
Test substance	:		
Deg. products CAS#	:		
Method	:		
Method detail	:		
Result	:		
Remark	:	**Supporting data for dissociation products:** **Acid:** Aerobic biodegradation of 2-ethylhexanoic acid was reported with BOD_5, BOD_{10} and BOD_{20} at 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (See Appendix I: 5.1.1).	
Reliability	:		
Reference	:		

3.7 BIOCONCENTRATION

Type	:		
Guideline/method	:		
Species	:		
Exposure period	:	at	°C
Concentration	:		
BCF	:		
Elimination	:		
Year	:		
GLP	:		
Test substance	:		
Method	:		
Method detail	:		
Result	:		
Remark	:		
Reliability	:		
Reference	:		

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h LC50 for fathead minnows (*Pimephales promelas*) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix I: 6.1.1).
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (See Appendix I: 6.2.1).
Reliability	:	
Reference	:	

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	
Guideline/method	:	
Species	:	
Endpoint	:	
Exposure period	:	
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h E_bC50 (EC50 based upon biomass) for the green alga *Scenedesmus subspicatus* was reported to be 40.616 mg/L for 2-ethylhexanoic acid (See Appendix I: 6.3).
Reliability	:	
Reference	:	

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:
Type	:
Guideline/method	:
Species	:
Number of animals	:
Males	:
Females	:
Doses	:
Males	:
Females	:
Vehicle	:
Route of administration	:
Exposure time	:
Product type guidance	:
Decision on results on acute tox. tests	:
Adverse effects on prolonged exposure	:
Half-lives	: 1st: 2nd: 3rd:
Toxic behavior	:
Deg. product	:
Deg. products CAS#	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:

Acid: Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed

by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid
		7% glucuronide-diacid or hydroxylated 2- Ethylhexanoic acid
		2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid
		14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid
		12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid
		3% glucuronide-diacid or

			hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
	Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :
Guideline/Method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (See Appendix I: 7.1.1).
Reliability :
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :

Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (See Appendix I: 7.1.2).
Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted) was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg.(See Appendix I: 7.1.3)
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation

Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1 (B))

Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours (See Appendix I: 7.2.2; note study is of low reliability).
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-

ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery.

Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Appendix I: 7.4(H)). These data are consistent with four previous repeated dose studies in Fischer rats (See Appendix I: 7.4).

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :

Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid either with or without activation (See Appendix I: 7.5.1).
Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (See Appendix I: 7.5.3).
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :

Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**

Acid: Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (See Appendix I: 7.7.2). In the most reliable study, the NOEL for teratogenic and developmental effects in rats for was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight were noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters was significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(See Appendix I: 7.2.2 (E and F))

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :

Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**

Acid: A One-Generation Reproduction Toxicity Study was conducted with 2-ethylhexanoic acid. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected

dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

(See Appendix I: 7.7.1)

Reliability :
Reference :

9.0 OTHER INFORMATION

9.1 **CARCINOGENICITY**

ROBUST SUMMARIES and

SIDS DOSSIER for:
2-Ethylhexanoic Acid

••••••••••••••••••••

CAS No. 149-57-5

Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

		Page
SIDS PROFILE		1
SIDS SUMMARY		2
1.0	GENERAL INFORMATION	4
2.0	CHEMICAL IDENTITY	4
	*2.1 CAS NUMBER	4
	*2.2 NAME	4
	2.3 COMMON SYNONYMS	4
	2.4 EMPIRICAL FORMULA	5
	*2.5 STRUCTURAL FORMULA	5
	2.6 PURITY OF INDUSTRIAL PRODUCT	5
	2.6.1 DEGREE OF PURITY	5
	2.6.2 IDENTITY OF MAJOR IMPURITIES	5
	2.6.3 ESSENTIAL ADDITIVES	5
3.0	PHYSICAL-CHEMICAL DATA	5
	*3.1 MELTING OR DECOMPOSITION POINT	5
	*3.2 BOILING POINT	5
	*3.3 VAPOR PRESSURE	6
	*3.4 PARTITION COEFFICIENT N-OCTANOL/WATER	6
	*3.5 WATER SOLUBILITY	7
	3.6 FLASH POINT (LIQUIDS)	7
	3.7 FLAMMABILITY	7
	3.8 PH IN WATER	8
	3.9 OTHER DATA	8
4.0	SOURCE OF EXPOSURE	8
	*4.1 PRODUCTION LEVELS EXPRESSED AS TONNES PER ANNUM	8
	4.2 PROCESSES	8
	*4.3 INFORMATION CONCERNING USES	8
	4.4 OPTIONS FOR DISPOSAL	8
	4.5 OTHER REMARKS	9
5.0	ENVIRONMENTAL FATE AND PATHWAYS	9
	5.1 DEGRADABILITY (BIOTIC AND ABIOTIC)	9
	5.1.1 BIODEGRADABILITY	9
	5.1.2 SEWAGE TREATMENT	10
	5.1.3 STABILITY IN AIR	10
	5.1.4 STABILITY IN WATER	10
	5.1.5 IDENTIFICATIN OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE	10
	5.2 BIOACCUMULATION	11
	5.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS	11
	5.4 MONITORING DATA	11
6.0	ECOTOXICOLOGICAL DATA	11
	6.1 TOXICITY TO FISH	11
	6.1.1 RESULTS OF ACUTE TESTS	11
	6.1.2 RESULTS OF LONG-TERM TESTS	12
	6.2 TOXICITY TO DAPHNIDS	13
	6.2.1 RESULTS OF ACUTE TESTS	13
	6.2.2 RESULTS OF LONG-TERM TESTS	13
	6.3 TOXICITY TO ALGAE	14
	6.4 TOXICITY TO OTHER AQUATIC ORGANISMS	14

Page
6.5 TOXICITY TO BACTERIA 15
*6.6 TOXICITY TO TERRESTRIAL ORGANISMS 15
6.6.1 TOXICITY TO SOIL DWELLING ORGANISMS 15
6.6.2 TOXICITY TO PLANTS 15
6.6.3 TOXICITY TO BIRDS 15
6.7 BIOLOGICAL EFFECTS MONITORING 15
6.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES 15
7.0 TOXICOLOGICAL DATA 15
7.1 ACUTE TOXICITY 15
7.1.1 ACUTE ORAL TOXICITY 16
7.1.2 ACUTE INHALATION TOXICITY 17
7.1.3 ACUTE DERMAL TOXICITY 18
7.2 CORROSIVENESS/IRRITATION 19
7.2.1 SKIN IRRITATION 19
7.2.2 EYE IRRITATION 20
7.3 SKIN SENSITISATION 20
*7.4 REPEATED DOSE TOXICITY 21
*7.5 GENETIC TOXICITY 27
7.5.1 BACTERIAL TEST 27
7.5.2 NON-BACTERIAL IN VITRO TEST 28
7.5.3 NON-BACTERIAL TEST IN VIVO 29
7.6 CARCINOGENICITY 29
*7.7 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY 30
7.7.1 REPRODUCTIVE TOXICITY 30
7.7.2 TERATOGENICITY/DEVELOPMENTAL TOXICITY 32
7.8 SPECIFIC TOXICITIES (NEUROTOXICITY, IMMUNOTOXICITY, ETC.) 41
7.9 TOXICODYNAMICS, TOXICO-KINETICS 41
8.0 EXPERIENCE WITH HUMAN EXPOSURE 43
8.1 BIOLOGICAL MONITORING 43
9.0 RECOMMENDED PRECAUTIONS, CLASSIFICATION, AND SAFETY DATA 44
10.0 AVAILABILITY AND REFERENCE(S) FOR EXISTING REVIEW(S) 44

APPENDIX A 45

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH(CH_2\text{-}CH_3)\text{-}C(=O)\text{-}OH$
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5 STUDY	Info. Available Y/N	OECD Study Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degrability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5 STUDY	Info Available Y/N	OECD Summary Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

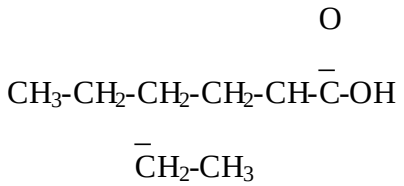
2.3 **Common Synonyms:**

a-Ethylcaproic acid
2-Ethylcaproic acid
a-Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**

$C_8H_{16}O_2$

* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **<u>Physical-Chemical Data</u>**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33 x 10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]

NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water** (Preferred Study)

log Pow = 3 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup [ ] open cup [X]

Method:

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 **pH in Water**

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES [ ]
NO [X]

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 **Other Data**

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 **Source of Exposure**

* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 **Other Remarks:**

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 Environmental Fate and Pathways

* 5.1 **Degradability (Biotic and Abiotic)**

5.1.1 **Biodegradability**

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic [ ]

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, J. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES [ ]
NO [X]

Test Results: BOD_5 = 60 % of Theoretical (2.44 g O_2/g test substance).
BOD_{10} = 76 % of Theoretical (2.44 g O_2/g test substance).
BOD_{20} = 83 % of Theoretical (2.44 g O_2/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 **Sewage Treatment**

Comments: No Data Available.

5.1.3 **Stability in Air** (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES [ ]

NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 **Stability in Water** (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES [ ]
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 **Identification of Main Mode of Degradability in Actual Use**

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES [ ]
NO [X]

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 <u>Ecotoxicological Data</u>

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static [X], semi-static [ ], flow-through [ ]
Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test Results: LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Daphnia magna (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES [ ]
NO [X]

Test Results: 48 hr EC_{50} = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC_0 = 62.5 mg/L, 48 hr EC_{100} = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC_0 - highest tested concentration without effect after 48 hours. EC_{100} - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengessellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES [ ]
NO [X]

Test Results: 72 hr EbC_{10} = 32.543 mg/L
72 hr EbC_{50} = 60.511 mg/L

96 hr EbC_{10} = 24.496 mg/L
96 hr EbC_{50} = 40.616 mg/L

72 hr EuC_{10} = 31.940 mg/L
72 hr EuC_{50} = 49.279 mg/L

96 hr EuC_{10} = 27.938 mg/L
96 hr EuC_{50} = 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

6.5 **Toxicity to Bacteria**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.6 **Toxicity to Terrestrial Organisms**

6.6.1 **Toxicity to Soil Dwelling Organisms**

Test Results: No Data Available.

6.6.2 **Toxicity to Plants**

Test Results: No Data Available.

6.6.3 **Toxicity to Birds**

Test Results: No Data Available.

6.7 **Biological Effects Monitoring (Including Biomagnification)**

Test Results: No Data Available.

6.8 **Biotransformation and Kinetics in Environmental Species**

No Data Available.

7.0 **<u>Toxicological Data</u>** (oral, dermal and inhalation, as appropriate)

* 7.1 **Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES [ ]
NO [X]

Test Results: Discriminating dose (for fixed dose only): LD_{50} = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES [X]
NO [ ]

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 **Acute Dermal Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES [ ]
NO [X]

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance**: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES [X]
NO [ ]

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 Eye Irritation

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES [ ]

NO [X]

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

7.3 Skin Sensitisation

Test Substance:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES [ ]
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES [ ]
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. Toxicol. Lett. 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed

consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized in extremis. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]

NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-

dose groups, respectively. One male from the mid-dose group was found dead during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and

mid-dose groups. Absolute and relative (to body weight) liver weight were significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes),

but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with

the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 Genetic Toxicity

7.5.1 Bacterial test

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: S. typhimurium TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES [ ]

NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES [ ]

NO [ ]

Test Results: No Data Available.

Comments:

Reference:

7.5.3 **Non-Bacterial Test *In Vivo***

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

GLP: YES [X]
NO [ ]

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

Comments: 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. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 **Carcinogenicity**

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]
NO [X]

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were

comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and Postnatal Development in Wistar Rats. Fundam. Appl. Toxicol. in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [ ]
NO [X]

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethyhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratol. 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES [ ]
NO [X]

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryolethality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryolethality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. Life Sci. 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES [ ]
NO [X]

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs

was significantly higher in the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in .the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. Fundam. Appl. Toxicol. 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrlBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour preiod; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

GLP: YES [ ]
NO [X]

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage of resorptions increased at higher dose levels, and was also high in the

animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. Toxicol. Appl. Pharmacol. 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose

group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]

NO [ ]

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption

by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(G.) **Teratogenicity/Developmental toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days (GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into three groups and fed diets as described for the second experiment. The

animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg)was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. Teratology 53(2):p88, Abstract 21.

7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

7.9 Toxicodynamics, Toxico-Kinetics

Test Substance: [2-^{14}C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmole) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO [ ]

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid

Oral	***100 mg/kg***	***12% glucuronide-2-Ethylhexanoic acid***
	(Repeated)	12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 **Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m^3 (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded

exposure to 0.5 ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid elimination of the material. No urine samples were collected during the work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be 2-2.33 x 10^{-4} mg/kilogram body weight/8 hour workday. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. Int. Arch. Occup. Environ. Health, 62:213-216.

9.0 Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 Availability and Reference(s) for Existing Review(s)

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

Note: Appendix I is Robust Summaries and SIDS Dossier for 2-ethylhexanoic acid

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, calcium salt
Chemical Name	:	Hexanoic acid, 2-ethyl, calcium salt
CAS Registry No.	:	136-51-6
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$C_{16}H_{30}CaO_4$
Molecular Weight	:	326.4906
Synonyms and Trade names	:	Calcium 2-ethylhexanoate; calcium octoate
References	:	http://www.chemfinder.com

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Melting point is reported as –118.4°C for 2-ethylhexanoic acid (See Appendix I: 3.1)
Reliability :
Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (See Appendix I.: 3.2)
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value : at °C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference

2.4 VAPOR PRESSURE

Type :

Guideline/method :
Value : hPa at °C
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Vapor pressure is reported as 1.33 x 10^{-3} kPa at 20°C for 2-ethylhexanoic acid (See Appendix I: 3.3)
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (See Appendix I: 3.4).
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The water solubility of 2-ethylhexanoic acid was reported to be 25

mg/L at 25°C (See Appendix I: 3.5).

Reliability :

Reference :

2.7 FLASH POINT

Type :

Guideline/method :

Value : °C

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark : **Supporting data for dissociation products:**
Acid: A flashpoint of 118°C was reported for 2-ethylhexanoic acid (See Appendix I: 3.6).

Reliability :

Reference :

3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Half-life (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.2 DISSOCIATION

Type : Dissociation constant determination
Guideline/method : OECD 112
pKb : 8.45 at 20°C
Year : 2002
GLP : Yes
Test substance : Calcium 2-ethylhexanoate, lot number 03818KU, received from Aldrich Chemical Company. White powder with lumps, purity of 12.5% calcium
Approximate water solubility : 1.0 mg/mL (1000 mg/L) as determined visually in preliminary study
Method : OECD Guideline 112, Dissociation Constants in Water
Method detail : Three replicate samples of calcium 2-ethylhexanoate were prepared at a nominal concentration of 500 mg/L by dissolving 0.050 grams of test substance in degassed water (ASTM Type II). Each sample was titrated against 0.001N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result : Mean (N = 3) pKb value was 8.45 (SD = 0.0380) at 20°C
Remark : The results indicate that dissociation of the test substance will occur at

environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of calcium 2-ethylhexanoate, Wildlife International, Ltd. Study No. 534C-107, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %

%

Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Aerobic biodegradation of 2-ethylhexanoic acid was reported with BOD_5, BOD_{10} and BOD_{20} at 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (See Appendix I: 5.1.1).
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	Acute toxicity to fish. Static exposure.
Guideline/method	:	
Species	:	*Lepomis macrochirus* (bluegill sunfish, freshwater)
Exposure period	:	96 hours
NOEC	:	
LC0	:	
LC50	:	LC50 greater than tested concentration (100% of a 5% calcium octoate solution)
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	Only tested 100% concentration of a 5% calcium octoate solution
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Calcium octoate, 5%, Lot no. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ). Reported as not soluble in water. Purity not reported
Method	:	United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	:	Test concentrations were control and 100% concentration of a 5% calcium octoate solution. Test conducted in reconstituted freshwater (hardness = soft water) and temperature range of 20 - 21ºC. Fish were < 1 year old and of same age class. Biological loading was 0.8 g/L.
Result	:	No mortality observed in 100% concentration of a 5% calcium octoate solution.
Remark	:	**Supporting data for dissociation products:** **Acid**: The 96-h LC50 for fathead minnows (*Pimephales promelas*) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix I: 6.1.1).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished, and no analytical verification of test concentrations. Lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

Type	:	Acute toxicity to fish. Static exposure.
Guideline/method	:	
Species	:	*Cyprinodon variegatus* (sheepshead minnow, saltwater)
Exposure period	:	96 hours
NOEC	:	
LC0	:	
LC50	:	LC50 greater than tested concentration (100% of a 5% calcium octoate solution)
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	Only tested 100% concentration of a 5% calcium octoate solution
Analytical monitoring	:	None reported

Year	:	1981
GLP	:	Not reported
Test substance	:	Calcium octoate, 5%, Lot no. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ). Reported as not soluble in water. Purity not reported
Method	:	United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	:	Test concentrations were control and 100% concentration of a 5% calcium octoate solution. Test conducted using synthetic seawater (28 ppt), temperature range of 19 - 22ºC, fish < 1 yr old and of same age class, biological loading 0.9 g/L.
Result	:	No mortality observed in 100% concentration of a 5% calcium octoate solution.
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h LC50 for fathead minnows (*Pimephales promelas*) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix I: 6.1.1).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished, and no analytical verification of test concentrations. Lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Acute toxicity to daphnids. Static exposure
Guideline/method	:	
Species	:	*Daphnia magna*
Exposure period	:	48 hours
NOEC	:	
EC0	:	
EC50	:	48-h EC50: 26.1% (95% CI: 21.3 – 32%)
EC100	:	
Other	:	24-h EC50: 79.6% (95% CI: 30.3 – 209.2%)
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Calcium octoate, 5%, Lot no. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ). Reported as not soluble in water. Purity not reported
Method	:	United States Testing Company protocol PRO/FT, Daphnia, 365-0
Method detail	:	Test conducted in filtered (0.22 µ) lake water (hardness = soft), temperature range 20 - 21ºC. Test concentrations were 0, 5.6, 10, 18, 32 and 56% of calcium octoate (5% solution). No information on test organisms.
Result	:	48-h EC50: 26.1% (95% CI: 21.3 – 32%); 24-h EC50: 79.6% (95% CI: 30.3 – 209.2%)
Remark	:	**Supporting data for dissociation products:** **Acid:** The 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (See Appendix I: 6.2.1).

Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished and no analytical verification of test concentrations. Lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	Algal acute toxicity test
Guideline/method	:	
Species	:	*Selenastrum capricorntum* (freshwater green alga)
Endpoint	:	„growth“ (not specified further)
Exposure period	:	96 hours
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	5.2%
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Calcium octoate, 5%, Lot no. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ). Reported as not soluble in water. Purity not reported
Method	:	United States Testing Company protocol PRO/FT, ALGAE, 357-0
Method detail	:	Test concentrations were 0, 5.6, 10, 18, 32 and 56%. Stock solution prepared by adding an excessive amount of calcium octoate (5%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used freshwater algal maintenance medium and test temperature 21 - 22ºC.
Result	:	96-h EC50 for was 5.2%
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h E_bC50 (EC50 based upon biomass) for the green alga *Scenedesmus subspicatus* was reported to be 40.616 mg/L for 2-ethylhexanoic acid (See Appendix I: 6.3).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Non-standard test conditions, lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

Type	:	Algal acute toxicity test
Guideline/method	:	
Species	:	*Skeletonema costatum* (saltwater diatom)

Endpoint	:	„growth“ (not specified further)
Exposure period	:	96 hours
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	26%
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Calcium octoate, 5%, Lot no. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ). Reported as not soluble in water. Purity not reported
Method	:	United States Testing Company protocol PRO/FT, ALGAE, 357-0
Method detail	:	Test concentrations were 0, 5.6, 10, 18, 32 and 56%. Stock solution prepared by adding an excessive amount of calcium octoate (5%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used seawater algal medium I and test temperature 19 - 20ºC
Result	:	96-h EC50 was 26%
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h E_bC50 (EC50 based upon biomass) for the green alga *Scenedesmus subspicatus* was reported to be 40.616 mg/L for 2-ethylhexanoic acid (See Appendix I: 6.3).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Non-standard test conditions, lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:
Type	:
Guideline/method	:
Species	:
Number of animals	:
Males	:
F emales	:
Doses	:
Males	:
Females	:
Vehicle	:
Route of administration	:
Exposure time	:
Product type guidance	:
Decision on results on acute tox. tests	:
Adverse effects on prolonged exposu re	:
Half-lives	: 1st: 2nd: 3rd:
Toxic behavior	:
Deg. product	:
Deg. products CAS#	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:

Acid: Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed

by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid
		7% glucuronide-diacid or hydroxylated 2- Ethylhexanoic acid
		2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid
		14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid
		12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid
		3% glucuronide-diacid or

			hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
	Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type : Limit test
Guideline/Method :
Species : Rat
Strain : Sherman-Wistar albino
Sex : Male and female
Number of animals : 10 (5 male, 5 female)
Vehicle :
Doses : One dose, 5 g/kg
LD50 : > 5 g/kg
Year : 1980
GLP : Not reported
Test substance : Calcium octoate, 5%, Lot no. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ). Purity not reported
Method : Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.
Method detail : Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation. Observed for 14-days post-exposure.
Result : No mortality seen. LD50 > 5g/kg. At 60-90 minutes following dosing, animals were slightly depressed and ruffled; after 18-24 hours, animals were severely depressed, dirty, ruffled and ataxic; at 48-72 hours, animals appeared improved; and they appeared recovered and essentially normal after 4 days. Gross necropsies were unremarkable.
Remark : **Supporting data for dissociation products:**
Acid: The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (See Appendix I: 7.1.1).
Reliability : [2] Reliable with restrictions. Basic data provided, exposure conditions not fully described. Comparable to guideline.
Reference : Biosearch, Inc., Philadelphia, PA. (Study No. 80-1975-A), study conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ.

5.1.2 ACUTE INHALATION TOXICITY

Type : Limit test
Guideline/method :
Species : Rat
Strain : Albino

Sex	:	Male and female
Number of animals	:	10 (5 male and 5 female)
Vehicle	:	
Doses	:	One concentration, 4.8 mg/L
Exposure time	:	1 hour
LC50	:	> 4.8 mg/L (maximum attainable nominal concentration)
Year	:	1980
GLP	:	Not reported
Test substance	:	Calcium octoate, 5%, Lot no. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ). Purity not reported
Method	:	
Method detail	:	Animals (205 – 210 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 72ºF. Test material concentration was measured and determined to be 4.8 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 1.3 microns MMD (mass median diameter). Animals observed for 14 days post-exposure
Result	:	No mortality, no toxicity, and no adverse gross necropsy findings
Remark	:	**Supporting data for dissociation products:** **Acid:** The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (See Appendix I: 7.1.2).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Exposure conditions not described; duration of exposure and determination of measured test concentrations less than current guidelines require.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study No. 80-1975-A), study conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ.

5.1.3 ACUTE DERMAL TOXICITY

Type	:	Limit test
Guideline/method	:	
Species	:	Rabbit
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	Six (3 male and 3 female)
Vehicle	:	
Doses	:	One dose, 5 g/kg
LD50	:	> 5 g/kg
Year	:	1980
GLP	:	Not reported
Test substance	:	Calcium octoate, 5%, Lot no. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ). Purity not reported
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.40.
Method detail	:	Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious damming. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure.
Result	:	No mortality or toxicity. Severe skin irritation lasting 10 days. No adverse

gross necropsy findings

Remark : **Supporting data for dissociation products:**
Acid: The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted) was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg.(See Appendix I: 7.1.3)

Reliability : [2] Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.

Reference : Biosearch, Inc., Philadelphia, PA. (Study No. 80-1975-A), study conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ.

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :

Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1 (B))

Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :

Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours (See Appendix I: 7.2.2; note study is of low reliability).
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery.

Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute

albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Appendix I: 7.4(H)). These data are consistent with four previous repeated dose studies in Fischer rats (See Appendix I: 7.4).

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Ames assay, standard plate assay
Species	:	*Salmonella typhimurium*
Strain	:	TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations	:	1, 10, 100, 500, and 1000 µg/plate, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254 per Ames et al., 1975, Mut. Res. 31:347-364. No further details.
Year	:	1980
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement.
Test substance	:	Calcium octoate 5%
Method	:	Followed method of Ames et. al.
Method detail	:	0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37ºC and number of colonies compared to background. No further details provided.
Result	:	Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of *S. typhimurium* tested, either with or without activation. Mutagenic index of all five strains was less than 2.0. Positive controls produced the expected response. Noted that two highest concentrations caused a white precipitate to form.
Remark	:	**Supporting data for dissociation products:**

Acid: In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid either with or without activation (See Appendix I: 7.5.1).

Reliability : [2] Reliable with restrictions. Basic data provided. Comparable to guideline.

Reference : Van Goethem, D., 1980. Evaluation of calcium octoate in the *Salmonella*/Microsome (Ames) Assay. Study conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

Type : Mutagenicity

Guideline/method :

System of testing : Bacterial DNA damage or repair assay

Species : *Escherichia coli*

Strain : W3110 (pol A^+) and its DNA polymerase deficient derivative p3478 (pol A^-)

Test concentrations : 5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in ethanol.

Cytotoxic concentr. :

Metabolic activation : With and without. Activation with S-9 from Aroclor 1254 induced rat liver per Ames al., 1975, Mut. Res. 31:347-364 .

Year : 1981

GLP : No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement

Test substance : Calcium octoate, 5%

Method : Followed method of Rosenkranz et al. (1971).

Method detail : Test material (5 concentrations) applied to cells in culture. Negative controls (DMSO) and vehicle controls (ethanol) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 ug/mL without activation and 2-aminofluorene at 200 ug/mL with activation). Bacteria (10^4) of each strain were exposed to the test material for 1 hour at 37ºC. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37ºC and the number of viable cells determined.

Result : Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A^- to pol A^+ survivors), with or without activation. Survival index at all nonprecipitating dose levels was greater than 0.80. Noted that highest concentration caused a white precipitate to form in the aqueous medium, hence data from this concentration not useful.

Remark :

Reliability : [2] Reliable with restrictions. Basic data provided. Comparable to guideline.

Reference : Van Goethem, D., 1981. Evaluation of calcium octoate, 5%, in the *E. coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

5.6 GENETIC TOXICITY 'IN VIVO'

Type :

Guideline/method :

Species :

Strain :

Sex :

Route of admin. :

Exposure period :

Doses :

Year :

GLP :

Test substance :

Method :

Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (See Appendix I: 7.5.3).
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (See Appendix I: 7.7.2). In the most reliable study, the NOEL for teratogenic and developmental effects in rats for was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight were noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters was significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(See Appendix I: 7.2.2 (E and F))

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:
Acid: A One-Generation Reproduction Toxicity Study was conducted with 2-ethylhexanoic acid. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall

toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

(See Appendix I: 7.7.1)

Reliability :
Reference :

10.0 OTHER INFORMATION

10.1 CARCINOGENICITY

APPENDIX I

ROBUST SUMMARIES and

SIDS DOSSIER for:
2-Ethylhexanoic Acid

••••••••••••••••••••

CAS No. 149-57-5

Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

		Page
SIDS PROFILE		1
SIDS SUMMARY		2
1.0	GENERAL INFORMATION	4
2.0	CHEMICAL IDENTITY	4
	*2.1 CAS NUMBER	4
	*2.2 NAME	4
	2.3 COMMON SYNONYMS	4
	2.4 EMPIRICAL FORMULA	5
	*2.5 STRUCTURAL FORMULA	5
	2.6 PURITY OF INDUSTRIAL PRODUCT	5
	2.6.1 DEGREE OF PURITY	5
	2.6.2 IDENTITY OF MAJOR IMPURITIES	5
	2.6.3 ESSENTIAL ADDITIVES	5
3.0	PHYSICAL-CHEMICAL DATA	5
	*3.1 MELTING OR DECOMPOSITION POINT	5
	*3.2 BOILING POINT	5
	*3.3 VAPOR PRESSURE	6
	*3.4 PARTITION COEFFICIENT N-OCTANOL/WATER	6
	*3.5 WATER SOLUBILITY	7
	3.6 FLASH POINT (LIQUIDS)	7
	3.7 FLAMMABILITY	7
	3.8 PH IN WATER	8
	3.9 OTHER DATA	8
4.0	SOURCE OF EXPOSURE	8
	*4.1 PRODUCTION LEVELS EXPRESSED AS TONNES PER ANNUM	8
	4.2 PROCESSES	8
	*4.3 INFORMATION CONCERNING USES	8
	4.4 OPTIONS FOR DISPOSAL	8
	4.5 OTHER REMARKS	9
5.0	ENVIRONMENTAL FATE AND PATHWAYS	9
	5.1 DEGRADABILITY (BIOTIC AND ABIOTIC)	9
	5.1.1 BIODEGRADABILITY	9
	5.1.2 SEWAGE TREATMENT	10
	5.1.3 STABILITY IN AIR	10
	5.1.4 STABILITY IN WATER	10
	5.1.5 IDENTIFICATIN OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE	10
	5.2 BIOACCUMULATION	11
	5.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS	11
	5.4 MONITORING DATA	11
6.0	ECOTOXICOLOGICAL DATA	11
	6.1 TOXICITY TO FISH	11
	6.1.1 RESULTS OF ACUTE TESTS	11
	6.1.2 RESULTS OF LONG-TERM TESTS	12
	6.2 TOXICITY TO DAPHNIDS	13
	6.2.1 RESULTS OF ACUTE TESTS	13
	6.2.2 RESULTS OF LONG-TERM TESTS	13
	6.3 TOXICITY TO ALGAE	14
	6.4 TOXICITY TO OTHER AQUATIC ORGANISMS	14

Page

6.5 TOXICITY TO BACTERIA 15
*6.6 TOXICITY TO TERRESTRIAL ORGANISMS 15
6.6.1 TOXICITY TO SOIL DWELLING ORGANISMS 15
6.6.2 TOXICITY TO PLANTS 15
6.6.3 TOXICITY TO BIRDS 15
6.7 BIOLOGICAL EFFECTS MONITORING 15
6.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES 15
7.0 TOXICOLOGICAL DATA 15
7.1 ACUTE TOXICITY 15
7.1.1 ACUTE ORAL TOXICITY 16
7.1.2 ACUTE INHALATION TOXICITY 17
7.1.3 ACUTE DERMAL TOXICITY 18
7.2 CORROSIVENESS/IRRITATION 19
7.2.1 SKIN IRRITATION 19
7.2.2 EYE IRRITATION 20
7.3 SKIN SENSITISATION 20
*7.4 REPEATED DOSE TOXICITY 21
*7.5 GENETIC TOXICITY 27
7.5.1 BACTERIAL TEST 27
7.5.2 NON-BACTERIAL IN VITRO TEST 28
7.5.3 NON-BACTERIAL TEST IN VIVO 29
7.6 CARCINOGENICITY 29
*7.7 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY 30
7.7.1 REPRODUCTIVE TOXICITY 30
7.7.2 TERATOGENICITY/DEVELOPMENTAL TOXICITY 32
7.8 SPECIFIC TOXICITIES (NEUROTOXICITY, IMMUNOTOXICITY, ETC.) 41
7.9 TOXICODYNAMICS, TOXICO-KINETICS 41
8.0 EXPERIENCE WITH HUMAN EXPOSURE 43
8.1 BIOLOGICAL MONITORING 43
9.0 RECOMMENDED PRECAUTIONS, CLASSIFICATION, AND SAFETY DATA 44
10.0 AVAILABILITY AND REFERENCE(S) FOR EXISTING REVIEW(S) 44

APPENDIX A 45

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH(CH_2\text{-}CH_3)\text{-}C(=O)\text{-}OH$
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5 STUDY	Info. Available Y/N	OECD Study Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degrability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5 STUDY	Info Available Y/N	OECD Summary Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

2.3 **Common Synonyms:**

a-Ethylcaproic acid
2-Ethylcaproic acid
a-Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**

$C_8H_{16}O_2$

* 2.5 **Structural Formula:**

$$\begin{array}{l} \qquad\qquad\qquad\qquad\quad O \\ CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH\text{-}\overline{C}\text{-}OH \\ \qquad\qquad \overline{C}H_2\text{-}CH_3 \end{array}$$

2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **<u>Physical-Chemical Data</u>**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33×10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]

NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water** (Preferred Study)

log Pow = 3 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup [ ] open cup [X]

Method:

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 **pH in Water**

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES [ ]
NO [X]

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 **Other Data**

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 **Source of Exposure**

* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 **Other Remarks:**

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 Environmental Fate and Pathways

* 5.1 **Degradability (Biotic and Abiotic)**

5.1.1 **Biodegradability**

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic [ ]

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, J. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES [ ]
NO [X]

Test Results: BOD_5 = 60 % of Theoretical (2.44 g O_2/g test substance).
BOD_{10} = 76 % of Theoretical (2.44 g O_2/g test substance).
BOD_{20} = 83 % of Theoretical (2.44 g O_2/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 **Sewage Treatment**

Comments: No Data Available.

5.1.3 **Stability in Air** (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES [ ]

NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 **Stability in Water** (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES [ ]
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 **Identification of Main Mode of Degradability in Actual Use**

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES [ ]
NO [X]

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 <u>Ecotoxicological Data</u>

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static [X], semi-static [ ], flow-through [ ]
Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test Results: LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Daphnia magna (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES [ ]
NO [X]

Test Results: 48 hr EC_{50} = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC_0 = 62.5 mg/L, 48 hr EC_{100} = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC_0 - highest tested concentration without effect after 48 hours. EC_{100} - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengessellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES [ ]
NO [X]

Test Results: 72 hr EbC_{10} = 32.543 mg/L
72 hr EbC_{50} = 60.511 mg/L

96 hr EbC_{10} = 24.496 mg/L
96 hr EbC_{50} = 40.616 mg/L

72 hr EuC_{10} = 31.940 mg/L
72 hr EuC_{50} = 49.279 mg/L

96 hr EuC_{10} = 27.938 mg/L
96 hr EuC_{50} = 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

6.5 **Toxicity to Bacteria**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.6 **Toxicity to Terrestrial Organisms**

6.6.1 **Toxicity to Soil Dwelling Organisms**

Test Results: No Data Available.

6.6.2 **Toxicity to Plants**

Test Results: No Data Available.

6.6.3 **Toxicity to Birds**

Test Results: No Data Available.

6.7 **Biological Effects Monitoring (Including Biomagnification)**

Test Results: No Data Available.

6.8 **Biotransformation and Kinetics in Environmental Species**

No Data Available.

7.0 **<u>Toxicological Data</u>** (oral, dermal and inhalation, as appropriate)

* 7.1 **Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES [ ]
NO [X]

Test Results: Discriminating dose (for fixed dose only): LD_{50} = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES [X]
NO [ ]

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 **Acute Dermal Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES [ ]
NO [X]

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance**: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES [X]
NO [ ]

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 Eye Irritation

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES [ ]

NO [X]

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

7.3 Skin Sensitisation

Test Substance:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES [ ]
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES [ ]
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. Toxicol. Lett. 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed

consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized in extremis. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]

NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-

dose groups, respectively. One male from the mid-dose group was found dead during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and

mid-dose groups. Absolute and relative (to body weight) liver weight were significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes),

but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with

the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 Genetic Toxicity

7.5.1 Bacterial test

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: S. typhimurium TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES [ ]

NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES [ ]

NO [ ]

Test Results: No Data Available.

Comments:

Reference:

7.5.3 **Non-Bacterial Test *In Vivo***

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

GLP: YES [X]
NO [ ]

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

Comments: 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. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 **Carcinogenicity**

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]
NO [X]

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were

comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and Postnatal Development in Wistar Rats. Fundam. Appl. Toxicol. in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [ ]
NO [X]

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethyhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratol. 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES [ ]
NO [X]

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryolethality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryolethality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. Life Sci. 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES [ ]
NO [X]

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs

was significantly higher in the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in .the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. Fundam. Appl. Toxicol. 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrlBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour preiod; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

GLP: YES [ ]
NO [X]

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage of resorptions increased at higher dose levels, and was also high in the

animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. Toxicol. Appl. Pharmacol. 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose

group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]

NO [ ]

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption

by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(G.) **Teratogenicity/Developmental toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days (GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into three groups and fed diets as described for the second experiment. The

animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg)was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. Teratology 53(2):p88, Abstract 21.

7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

7.9 Toxicodynamics, Toxico-Kinetics

Test Substance: [2-^{14}C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmole) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO [ ]

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid
Oral	***100 mg/kg*** (Repeated)	***12% glucuronide-2-Ethylhexanoic acid*** 12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid

		5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 **Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m^3 (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid

elimination of the material. No urine samples were collected during the work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be 2-2.33 x 10^{-4} mg/kilogram body weight/8 hour workday. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. Int. Arch. Occup. Environ. Health, 62:213-216.

9.0 Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 Availability and Reference(s) for Existing Review(s)

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

Note: Appendix I is Robust Summaries and SIDS Dossier for 2-ethylhexanoic acid.

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, cobalt salt
Chemical Name	:	Hexanoic acid, 2-ethyl, cobalt (2+) salt
CAS Registry No.	:	136-52-7
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$C_{16}H_{30}CoO_4$
Molecular Weight	:	395.3438
Synonyms and Tradenames	:	Cobalt 2-ethylhexanoate; Cobalt octoate
References	:	http://www.chemfinder.com; MSDS prepared by The Shepherd Chemical Company, dated 3/26/02.

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Melting point is reported as –118.4°C for 2-ethylhexanoic acid (See Appendix I: 3.1
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Cobalt 2-ethylhexanoate, blue semi-solid, 17% Co by weight.
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (See Appendix I.: 3.2)
Reliability	:	
Reference	:	MSDS dated 3/26/02, prepared by The Shepherd Chemical Company

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	Not applicable
Year	:	
GLP	:	
Test substance	:	Cobalt 2-ethylhexanoate, blue semi-solid, 17% Co by weight
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference		MSDS dated 3/26/02, prepared by The Shepherd Chemical Company

2.4 VAPOR PRESSURE

Type	:	

Guideline/method	:	
Value	:	Not applicable
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Cobalt 2-ethylhexanoate, blue semi-solid, 17% Co by weight
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Vapor pressure is reported as 1.33 x 10^{-3} kPa at 20°C for 2-ethylhexanoic acid (See Appendix I: 3.3)
Reliability	:	
Reference	:	MSDS dated 3/26/02, prepared by The Shepherd Chemical Company

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (See Appendix I: 3.4).
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	Negligible
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	Cobalt 2-ethylhexanoate, blue semi-solid, 17% Co by weight
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The water solubility of 2-ethylhexanoic acid was reported to be 25

		mg/L at 25°C (See Appendix I: 3.5).
Reliability	:	
Reference	:	MSDS dated 3/26/02, prepared by The Shepherd Chemical Company

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	Not applicable
Year	:	
GLP	:	
Test substance	:	Cobalt 2-ethylhexanoate, blue semi-solid, 17% Co by weight
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** A flashpoint of 118°C was reported for 2-ethylhexanoic acid (See Appendix I: 3.6).
Reliability	:	
Reference	:	MSDS dated 3/26/02, prepared by The Shepherd Chemical Company

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	6.41 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Cobalt (II) 2-ethylhexanoate, lot number LB1736-40, received from Shepherd Chemical Company. Blue solid, purity of 17.0% cobalt.
Approximate water solubility	:	50 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of cobalt (II) 2-ethylhexanoate were prepared at a nominal concentration of 25 mg/L by fortification of 100 mL degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.002 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the first equivalence point (with one exception) and the titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 10 points (with one exception) on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKa value was 6.41 (SD = 0.0645) at 20°C

Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of cobalt (II) 2-ethylhexanoate, Wildlife International, Ltd. Study No. 534C-105, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	mg/l
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %
Control substance	:	

Kinetic	:	% %
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Aerobic biodegradation of 2-ethylhexanoic acid was reported with BOD_5, BOD_{10} and BOD_{20} at 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (See Appendix I: 5.1.1). **Metal: NA**
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type	:	Acute toxicity to fish. Static exposure.
Guideline/method	:	
Species	:	*Lepomis macrochirus* (bluegill sunfish, freshwater)
Exposure period	:	96 hours
NOEC	:	
LC0	:	
LC50	:	LC50 greater than tested concentration (100% of a 12% cobalt octoate solution).
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Cobalt octoate (12%), Lot No. 28702, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Light yellow liquid, mineral spirits odor. Purity and solubility not reported.
Method	:	United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	:	Test concentrations were control and 100% concentration of a 12% cobalt octoate solution. Test conducted in reconstituted freshwater (hardness = soft water) and temperature range of 20 – 21ºC. Fish were < 1 year old and of same age class. Biological loading was 0.8 g/L
Result	:	No mortality observed in 100% concentration of a 12% calcium octoate solution.
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h LC50 for fathead minnows (*Pimephales promelas*) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix I: 6.1.1). **Metal:** For cobalt chloride, the 96-h LC50 was 333 mg/L for *Cyprinus carpio* and 1,406 mg/L for *Oncorhynchus mykiss* (ECOTOX data base).
Reliability	:	[3] Not reliable. Test material inadequately described. Lack of detail on methods. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Secondary reference, which contains apparent typographical error in description of test concentrations.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

Type	:	Acute toxicity to fish. Static exposure.
Guideline/method	:	
Species	:	*Cyprinodon variegatus* (sheepshead minnow, saltwater)
Exposure period	:	96 hours
NOEC	:	
LC0	:	
LC50	:	LC50 greater than tested concentration (100% of a 12% cobalt octoate solution).
LC100	:	
Other	:	
Other	:	

Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Cobalt octoate (12%), Lot No. 28702, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Light yellow liquid, mineral spirits odor. Purity and solubility not reported.
Method	:	United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	:	Test concentrations were control and 100% concentration of a 12% cobalt octoate solution. Test conducted using synthetic seawater (28 ppt), temperature range of 19 - 22ºC, fish < 1 yr old and of same age class, biological loading 0.9 g/L.
Result	:	No mortality observed in 100% concentration of a 24% calcium octoate solution, for either species.
Remark	:	
Reliability	:	[3] Not reliable. Test material inadequately described. Lack of detail on methods. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Acute toxicity to daphnids. Static exposure.
Guideline/method	:	
Species	:	*Daphnia magna*
Exposure period	:	48 hours
NOEC	:	
EC0	:	
EC50	:	48-h EC50: 23% (95% CI: 15.3 – 34.5%)
EC100	:	
Other	:	24-h EC50 could not be estimated because of insufficient mortality. 24-h EC50 > 32%
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Cobalt octoate (12%), Lot No. MCI #51-117099, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Blue-violet liquid, reported as insoluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Daphnia, 365-0
Method detail	:	Test conducted in filtered (0.22 µ) lake water (hardness = soft), temperature range 20 - 21ºC. Test concentrations were 0, 3.2, 10, 18 and 32% of cobalt octoate (12% solution). No information on test organisms.
Result	:	48-h EC50: 23% (95% CI: 15.3 – 34.5%); 24-h EC50: could not be calculated because of low mortality
Remark	:	**Supporting data for dissociation products:** **Acid:** The 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (See Appendix I: 6.2.1).

		Metal: For cobalt chloride, reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished and no analytical verification of test concentrations. Lack of detail on methods. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	Algal acute toxicity test
Guideline/method	:	
Species	:	*Selenastrum capricornutum* (freshwater green alga)
Endpoint	:	„growth“ (not specified further; could be growth rate, yield or viability)
Exposure period	:	96 hours
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	0.03%
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Cobalt octoate (12%), Lot No. MCI #51-117099, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Blue-violet liquid, reported as insoluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Algae, 357-0
Method detail	:	Test concentrations were 0, 0.02, 0.03, 0.06, 0.10 and 0.18%. Stock solution prepared by adding an excessive amount of cobalt octoate (12%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used freshwater algal maintenance medium and test temperature 21 - 22ºC.
Result	:	96-h EC50 for was 0.03%. Confidence limits not reported.
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h E_bC50 (EC50 based upon biomass) for the green alga *Scenedesmus subspicatus* was reported to be 40.616 mg/L for 2-ethylhexanoic acid (See Appendix I: 6.3). **Metal:** For cobalt chloride, the 96-h EC50 for *Chlorella vulgaris* was 0.522 mg/L (ECOTOX data base).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard test conditions, lack of detail on methods. Secondary reference.

		lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.
Type	:	Algal acute toxicity test
Guideline/method	:	
Species	:	*Skeletonema costatum* (saltwater diatom)
Endpoint	:	„growth“ (not specified further; could be growth rate, yield or viability)
Exposure period	:	96 hours
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	15.0%
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Cobalt octoate (12%), Lot No. MCI #51-117099, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Blue-violet liquid, reported as insoluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Algae, 357-0
Method detail	:	Test concentrations were 0, 0.02, 0.03, 0.06, 0.10 and 0.18%. Stock solution prepared by adding an excessive amount of cobalt octoate (12%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used seawater algal medium I and test temperature 19 - 20ºC
Result	:	96-h EC50 was 15.0%. Confidence limits not reported.
Remark	:	
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard test conditions, lack of detail on methods. Reported EC50 extrapolated well beyond range of test concentrations. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.4 ACUTE TOXICITY TO AVIAN SPECIES

Type	:	Acute oral toxicity
Guideline/method	:	
Species	:	Bobwhite quail (*Colinus virginianus*)
Number, sex and age of animals	:	35 birds (16 males and 19 females), approximately 16 weeks old (200 ± 40 g)

Exposure period	:	14 days
NOEL	:	
LD50	:	Not stated, but less than half the birds died at the highest dose, therefore the LD50 would be > 2000 mg/kg.
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	No
Test substance	:	Cobalt octoate, in corn oil vehicle
Method	:	
Method detail	:	Birds were housed in metal cages with wire floors, under a photoperiod of 17 hours light and 7 hours dark, mean humidity of 66% and mean temperature of 20°C (range 13 - 28°C). Birds were provided with water and standard diet ad libitum (except overnight starvation prior to dosing). Dose levels included vehicle control, 1000 mg/kg and 2000 mg/kg, administered by oral gavage. Mortalities were recorded daily. Body weights were recorded prior to dosing and at days 3, 7 and 14. Food consumption was recorded weekly. All birds were examined at death or test termination for gross pathology.
Result	:	Birds dosed at 1000 mg/kg showed no toxic effects immediately after dosing, but one bird was dead within 24 hours and surviving birds had become quiet. No further ill effects were observed in any birds after day 2 of the study. Birds dosed at 2000 mg/kg were quiet after dosing, but surviving birds appeared normal within 19 hours after dosing. In this group, 4 birds died over the course of the study. In exposed birds, large bodyweight decreases were observed during days 0 to 3 following dosing and continued at the higher dose for days 3 to 7. However both exposed groups showed an increase in food consumption over days 7 to 14, with concurrent mean bodyweight increases.
Remark	:	
Reliability	:	[3] Not reliable. Test material inadequately described. Secondary reference, with mortalities by day not presented.
Reference	:	Previously abstracted information from studies conducted by Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. Original study report not available.

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:
Type	:
Guideline/method	:
Species	:
Number of animals	:
Males	:
Females	:
Doses	:
Males	:
Females	:
Vehicle	:
Route of administration	:
Exposure time	:
Product type guidance	:
Decision on results on acute tox. tests	:
Adverse effects on prolonged exposure	:
Half-lives	: 1st: 2nd: 3rd:
Toxic behavior	:
Deg. product	:
Deg. products CAS#	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs.

manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2- Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid 12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid

9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
2% unmetabolized 2-Ethylhexanoic acid

Metal: Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. Clin. Tox. 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type	:	Acute Oral (LD50) Toxicity
Guideline/Method	:	
Species	:	Rat
Strain	:	Sherman-Wistar albino
Sex	:	Male and female
Number of animals	:	Nine groups of 10 (5 male, 5 female)
Vehicle	:	
Doses	:	0.63, 0.79, 1.00, 1.26, 1.58, 2.00, 2.51, 3.16, 3.98 g/kg
LD50	:	For males: 1.55 g/kg (95% CI: 1.26 – 1.86 g/kg) For females: 1.22 g/kg (95% CI: 1.03 – 1.48 g/kg)
Year	:	1980
GLP	:	Not reported
Test substance	:	Cobalt octoate, 12%, (MC1 #51-11709), supplied by sponsor. Density approximately 1.02 g/mL.
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.
Method detail	:	Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation. Observed for 14-days post-exposure.
Result	:	No symptoms were observed at the lowest dose. At intermediate doses, several animals died but surviving animals appeared to recover fully. All of the animals dosed at the three highest levels were dead within 24 hours. At doses of 2.51 g/kg and higher, animals were severely depressed, ataxic, ruffled, and drooling within 30 minutes of dosing; after 45-60 minutes they were comatose and most deaths occurred within 2-5 hours. Gross necropsies were unremarkable.
Remark	:	**Supporting data for dissociation products:** **Acid:** The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (See Appendix I: 7.1.1). **Metal:** Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to

cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg CoCl2/kg bw (equivalent to 19.1 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate was reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 55.4 to 72.5 mg Co/kg bw) (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 55.4 mg/kg bw when expressed as cobalt (ATSDR Sept 2001 Draft).

Reliability : [2] Reliable with restrictions. Basic data provided, exposure conditions not fully described, test material not described. Comparable to guideline.

Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), study conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.2 ACUTE INHALATION TOXICITY

Type : Limit Test

Guideline/method :

Species : Rat

Strain : Albino

Sex : Male and female

Number of animals : 10 rats (5 male and 5 female in each group)

Vehicle :

Doses : One concentration, 10.0 mg/L of a 50% w/v suspension in mineral spirits. Median particle diameter measured to ensure a respirable dose was received.

Exposure time : 1 hour

LC50 : > 10.0 mg/L (maximum attainable nominal concentration)

Year : 1980

GLP : Not reported

Test substance : Cobalt octoate 12% (MC1 #51-11709), prepared and used as a 50% w/v suspension in mineral spirits.

Method :

Method detail : Animals (200 – 205 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 72ºF. Test material concentration was measured and determined to be 10.0 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 0.82 microns MMD (mass median diameter). Animals observed for 14 days post-exposure

Result : No adverse effects were observed during the exposure period or during the two-week post exposure period. No mortality, no toxicity, and no adverse gross necropsy findings

Remark : **Supporting data for dissociation products:**
Acid: The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (See Appendix I: 7.1.2).
Metal: The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m^3 as mixed cobalt oxides. (ATSDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was >10 mg/L (IUCLID, 2000).

Reliability : [2] Reliable with restrictions. Basic data provided. Exposure conditions not described, duration of exposure and determination of measured test concentrations less than current guidelines require.

Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.3 ACUTE DERMAL TOXICITY

Type	:	Limit Test
Guideline/method	:	
Species	:	Rabbit
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	Six (3 male and 3 female)
Vehicle	:	
Doses	:	One dose, 5 g/kg
LD50	:	> 5 g/kg
Year	:	1980
GLP	:	Not reported
Test substance	:	Cobalt octoate, 12%, MC1 #51-11709, supplied by sponsor. Density approx. 1.02 g/mL.
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.40.
Method detail	:	Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious damming. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure. Gross autopsies conducted on all dead and surviving animals.
Result	:	No mortality. Substantial skin irritation lasting several days was observed. No adverse gross necropsy findings in this limit test.
Remark	:	**Supporting data for dissociation products:** **Acid:** The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted) was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg.(See Appendix I: 7.1.3). **Metal:** Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.1 SKIN IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	

Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1(B)).
Metal: Cobalt is reported to be irritating to the skin (IUCLID, 2000).
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours (See Appendix I: 7.2.2; note study was of low reliability).
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :

NOAEL	:
LOAEL	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery.

Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Appendix I: 7.4(H)). These data are consistent with four previous repeated dose studies in

Fischer rats (See Appendix I: 7.4).

Metal: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).

Reliability :

Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Ames assay, standard plate assay
Species	:	*Salmonella typhimurium*
Strain	:	TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations	:	5, 10, 50, 100, and 500 µg/plate, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254, as per Ames et al., 1975, Mut. Res. 31:347-364. No further details.
Year	:	1980
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Cobalt octoate 12% (12.1), MCI No. 51-11709; dark purple liquid
Method	:	Followed method of Ames et. al.
Method detail	:	0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37ºC and number of colonies compared to background. No further details provided.
Result	:	Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of *S. typhimurium* tested, either with or without activation. Mutagenic index of all five strains was less than 2.0. Positive controls produced the expected response. Precipitate formed at highest dose level.
Remark	:	**Supporting data for dissociation products:** **Acid:** In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid, either with or without activation (See Appendix I: 7.5.1). **Metal:** Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be generally non-mutagenic in bacterial assays, but increased frequency of genetic conversions have been reported in yeast. Cobalt compounds with a valence state of III were weakly mutagenic in bacterial systems (ATSDR Sept 2001 Draft).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Van Goethem, D., 1980. Evaluation of cobalt octoate in the *Salmonella*/Microsome (Ames) assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

4822-E).

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Bacterial DNA damage or repair assay
Species	:	*Escherichia coli*
Strain	:	W3110 (pol A^+) and its DNA polymerase deficient derivative p3478 (pol A^-)
Test concentrations	:	5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:	
Metabolic activation	:	With and without. Activation with S-9 from Aroclor 1254 induced rat liver as per Ames al., 1975, Mut. Res. 31:347-364
Year	:	1981
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Cobalt octoate 12% (12.1), MCI No. 51-11709; dark purple liquid
Method	:	Followed method of Rosenkranz et al. (1971).
Method detail	:	Test material (5 concentrations) applied to cells in culture. Vehicle controls (ethanol) and negative controls (DMSO) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 ug/mL without activation and 2-aminofluorene at 200 ug/mL with activation). Bacteria (10^4) of each strain were exposed to the test material for 1 hour at 37ºC. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37ºC and the number of viable cells determined.
Result	:	Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A^- to pol A^+ survivors), with or without activation. Survival index at all dose levels was greaten than 0.80. A precipitate formed at the highest dose level which confounds the interpretation of results at this level.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Van Goethem, D., 1981. Evaluation of cobalt in the *E.coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus mutagenicity assay
Guideline/method	:	
Species	:	Mouse
Strain	:	Specific Pathogen Free mice of the COBS CD-1 (ICR) BR (ICR derived) strain
Sex	:	Male and female
Number of animals	:	5 males and 5 females per dose level (including vehicle control and positive control)
Route of admin.	:	Oral gavage, using corn oil vehicle
Exposure period	:	Thirty hours (dosing at 0 and 24 hours, followed by 6 hours observation)
Doses	:	625, 1250 and 2500 mg/kg, given twice (24 hours apart) to produce total dose levels of 1250, 2500 and 5000 mg/kg. Corn oil control (0.1 mL/10g via gavage) and Mitomycin C positive control (injected i.p. at 4 mg/kg two times for a total dose of 8 mg/kg).
Year	:	1981
GLP	:	Yes
Test substance	:	Cobalt octoate (12%), [Cobalt 2-ethylhexanoate (12%)], batch #MCI 51-11709; clear dark purple liquid, specific gravity 1.01.
Method	:	No significant increases in the incidence of micronuclei in polychromatic

eryrthrocytes was seen in mice receiving 2-ethylhexanol, a compound closely related to 2-ethylhexanoic acid (See Appendix I: 7.5.3)

Method detail : Preliminary toxicity study was used to select upper dose for micronucleus test. Animals (18 – 21 g) fasted overnight and orally dosed (two doses, 24 hours apart). Standard volume per dose was 0.1 mL/10 g body weight. At the lowest dose, temporary lethargy was observed. Toxic symptoms (pilo-erection and lethargy at 2500 mg/kg and these symptoms plus hypopnea at 5000 mg/kg) were observed one-half hour after dosing but were not evident several hours later. Two deaths occurred at the highest dose. At the end of 30 hours, all animals were sacrificed. Femurs were cleared and one epiphysis removed from each bone; a bone marrow smear was made onto a slide containing calf serum, cleaned in methanol for 24 hours, air dried, fixed in methanol overnight, air dried, placed in buffer distilled water and stained with Giemsa. The number of micronucleated cells per 1000 polychromatic erythrocytes per animal and the rate of normochromatic to polychromatic erythrocytes was determined. Comparisons to control were made using Wilcoxon's Sum of Ranks test at p>0.10.

Result : No evidence of mutagenic potential was found. Test material groups produced micronucleated cell counts comparable to the vehicle control and to historical controls (0.1 – 1.8). Positive control response indicated a mean of 78.1 micronucleated cells per 1000 polychromatic erythrocytes. Ratio of normochromatic to polychromatic erythrocytes was comparable in test material and vehicle control groups (1.52). The positive control gave an increased ratio of 8.53.

Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (See Appendix I: 7.5.3).
Metal: Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (as cobalt chloride) (NOEL) (ATSDR Sept 2001 Draft).

Reliability : [2] Reliable with restrictions. Comparable to guideline. Incomplete description of test material.

Reference : Richold, M., and Richardson, J.C., 1981. Micronucleus test on Cobalt Octoate 12% [Cobalt 2-ethylhexanoate (12%)], study conducted for Tenneco Chemicals, Inc. by Huntingdon Research Centre, Huntingdon, England.

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :

NOAEL teratogen.	:
Other	:
Other	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (See Appendix I: 7.7.2). In the most reliable study, the NOEL for teratogenic and developmental effects in rats for was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal

occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(See Appendix I: 7.2.2 (E and F)

Metal: In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).

during gestation days 8-12 (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:
Acid: A One-Generation Reproduction Toxicity Study was conducted with 2-ethylhexanoic acid. Male and female Wistar rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body

weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

(See Appendix I: 7.7.1)

Metal: Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).

Reliability :

Reference :

11.0 OTHER INFORMATION

11.1 **CARCINOGENICITY** The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). “No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt.” (ATSDR Sept 2001 Draft).

ROBUST SUMMARIES and

SIDS DOSSIER for:
2-Ethylhexanoic Acid

••••••••••••••••••••

CAS No. 149-57-5

Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

		Page
SIDS PROFILE		1
SIDS SUMMARY		2
1.0	GENERAL INFORMATION	4
2.0	CHEMICAL IDENTITY	4
	*2.1 CAS NUMBER	4
	*2.2 NAME	4
	2.3 COMMON SYNONYMS	4
	2.4 EMPIRICAL FORMULA	5
	*2.5 STRUCTURAL FORMULA	5
	2.6 PURITY OF INDUSTRIAL PRODUCT	5
	2.6.1 DEGREE OF PURITY	5
	2.6.2 IDENTITY OF MAJOR IMPURITIES	5
	2.6.3 ESSENTIAL ADDITIVES	5
3.0	PHYSICAL-CHEMICAL DATA	5
	*3.1 MELTING OR DECOMPOSITION POINT	5
	*3.2 BOILING POINT	5
	*3.3 VAPOR PRESSURE	6
	*3.4 PARTITION COEFFICIENT N-OCTANOL/WATER	6
	*3.5 WATER SOLUBILITY	7
	3.6 FLASH POINT (LIQUIDS)	7
	3.7 FLAMMABILITY	7
	3.8 PH IN WATER	8
	3.9 OTHER DATA	8
4.0	SOURCE OF EXPOSURE	8
	*4.1 PRODUCTION LEVELS EXPRESSED AS TONNES PER ANNUM	8
	4.2 PROCESSES	8
	*4.3 INFORMATION CONCERNING USES	8
	4.4 OPTIONS FOR DISPOSAL	8
	4.5 OTHER REMARKS	9
5.0	ENVIRONMENTAL FATE AND PATHWAYS	9
	5.1 DEGRADABILITY (BIOTIC AND ABIOTIC)	9
	5.1.1 BIODEGRADABILITY	9
	5.1.2 SEWAGE TREATMENT	10
	5.1.3 STABILITY IN AIR	10
	5.1.4 STABILITY IN WATER	10
	5.1.5 IDENTIFICATIN OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE	10
	5.2 BIOACCUMULATION	11
	5.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS	11
	5.4 MONITORING DATA	11
6.0	ECOTOXICOLOGICAL DATA	11
	6.1 TOXICITY TO FISH	11
	6.1.1 RESULTS OF ACUTE TESTS	11
	6.1.2 RESULTS OF LONG-TERM TESTS	12
	6.2 TOXICITY TO DAPHNIDS	13
	6.2.1 RESULTS OF ACUTE TESTS	13
	6.2.2 RESULTS OF LONG-TERM TESTS	13
	6.3 TOXICITY TO ALGAE	14
	6.4 TOXICITY TO OTHER AQUATIC ORGANISMS	14

Page

6.5 TOXICITY TO BACTERIA 15
*6.6 TOXICITY TO TERRESTRIAL ORGANISMS 15
6.6.1 TOXICITY TO SOIL DWELLING ORGANISMS 15
6.6.2 TOXICITY TO PLANTS 15
6.6.3 TOXICITY TO BIRDS 15
6.7 BIOLOGICAL EFFECTS MONITORING 15
6.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES 15
7.0 TOXICOLOGICAL DATA 15
7.1 ACUTE TOXICITY 15
7.1.1 ACUTE ORAL TOXICITY 16
7.1.2 ACUTE INHALATION TOXICITY 17
7.1.3 ACUTE DERMAL TOXICITY 18
7.2 CORROSIVENESS/IRRITATION 19
7.2.1 SKIN IRRITATION 19
7.2.2 EYE IRRITATION 20
7.3 SKIN SENSITISATION 20
*7.4 REPEATED DOSE TOXICITY 21
*7.5 GENETIC TOXICITY 27
7.5.1 BACTERIAL TEST 27
7.5.2 NON-BACTERIAL IN VITRO TEST 28
7.5.3 NON-BACTERIAL TEST IN VIVO 29
7.6 CARCINOGENICITY 29
*7.7 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY 30
7.7.1 REPRODUCTIVE TOXICITY 30
7.7.2 TERATOGENICITY/DEVELOPMENTAL TOXICITY 32
7.8 SPECIFIC TOXICITIES (NEUROTOXICITY, IMMUNOTOXICITY, ETC.) 41
7.9 TOXICODYNAMICS, TOXICO-KINETICS 41
8.0 EXPERIENCE WITH HUMAN EXPOSURE 43
8.1 BIOLOGICAL MONITORING 43
9.0 RECOMMENDED PRECAUTIONS, CLASSIFICATION, AND SAFETY DATA 44
10.0 AVAILABILITY AND REFERENCE(S) FOR EXISTING REVIEW(S) 44

APPENDIX A 45

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH(CH_2\text{-}CH_3)\text{-}C(=O)\text{-}OH$
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5 STUDY	Info. Available Y/N	OECD Study Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degrability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5 STUDY	Info Available Y/N	OECD Summary Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

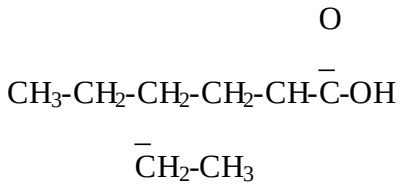
2.3 **Common Synonyms:**

a-Ethylcaproic acid
2-Ethylcaproic acid
a-Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**

$C_8H_{16}O_2$

* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **<u>Physical-Chemical Data</u>**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33×10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]

NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water** (Preferred Study)

log Pow = 3 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup [ ] open cup [X]

Method:

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 **pH in Water**

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES [ ]
NO [X]

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 **Other Data**

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 **Source of Exposure**

* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 **Other Remarks:**

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 Environmental Fate and Pathways

* 5.1 **Degradability (Biotic and Abiotic)**

5.1.1 **Biodegradability**

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic [ ]

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, J. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES [ ]
NO [X]

Test Results: BOD_5 = 60 % of Theoretical (2.44 g O_2/g test substance).
BOD_{10} = 76 % of Theoretical (2.44 g O_2/g test substance).
BOD_{20} = 83 % of Theoretical (2.44 g O_2/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 **Sewage Treatment**

Comments: No Data Available.

5.1.3 **Stability in Air** (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES [ ]

NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 **Stability in Water** (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES [ ]
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 **Identification of Main Mode of Degradability in Actual Use**

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES [ ]
NO [X]

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 <u>Ecotoxicological Data</u>

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static [X], semi-static [ ], flow-through [ ]
Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test Results: LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Daphnia magna (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES [ ]
NO [X]

Test Results: 48 hr EC_{50} = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC_0 = 62.5 mg/L, 48 hr EC_{100} = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC_0 - highest tested concentration without effect after 48 hours. EC_{100} - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengessellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES [ ]
NO [X]

Test Results: 72 hr EbC_{10} = 32.543 mg/L
72 hr EbC_{50} = 60.511 mg/L

96 hr EbC_{10} = 24.496 mg/L
96 hr EbC_{50} = 40.616 mg/L

72 hr EuC_{10} = 31.940 mg/L
72 hr EuC_{50} = 49.279 mg/L

96 hr EuC_{10} = 27.938 mg/L
96 hr EuC_{50} = 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

6.5 **Toxicity to Bacteria**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.6 **Toxicity to Terrestrial Organisms**

6.6.1 **Toxicity to Soil Dwelling Organisms**

Test Results: No Data Available.

6.6.2 **Toxicity to Plants**

Test Results: No Data Available.

6.6.3 **Toxicity to Birds**

Test Results: No Data Available.

6.7 **Biological Effects Monitoring (Including Biomagnification)**

Test Results: No Data Available.

6.8 **Biotransformation and Kinetics in Environmental Species**

No Data Available.

7.0 **<u>Toxicological Data</u>** (oral, dermal and inhalation, as appropriate)

* 7.1 **Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES [ ]
NO [X]

Test Results: Discriminating dose (for fixed dose only): LD_{50} = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES [X]
NO [ ]

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 **Acute Dermal Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES [ ]
NO [X]

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance**: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES [X]
NO [ ]

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 Eye Irritation

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES [ ]

NO [X]

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

7.3 Skin Sensitisation

Test Substance:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES [ ]
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES [ ]
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. Toxicol. Lett. 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed

consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized in extremis. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]

NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-

dose groups, respectively. One male from the mid-dose group was found dead during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and

mid-dose groups. Absolute and relative (to body weight) liver weight were significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes),

but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with

the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 Genetic Toxicity

7.5.1 Bacterial test

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: S. typhimurium TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES [ ]

NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES [ ]

NO [ ]

Test Results: No Data Available.

Comments:

Reference:

7.5.3 **Non-Bacterial Test *In Vivo***

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

GLP: YES [X]
NO [ ]

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

Comments: 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. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 **Carcinogenicity**

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]
NO [X]

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were

comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and Postnatal Development in Wistar Rats. Fundam. Appl. Toxicol. in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [ ]
NO [X]

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethyhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratol. 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES [ ]
NO [X]

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryolethality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryolethality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. Life Sci. 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES [ ]
NO [X]

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs

was significantly higher in the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in .the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. Fundam. Appl. Toxicol. 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrlBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour preiod; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

GLP: YES [ ]
NO [X]

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage of resorptions increased at higher dose levels, and was also high in the

animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. Toxicol. Appl. Pharmacol. 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose

group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]

NO [ ]

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption

by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(G.) **Teratogenicity/Developmental toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days (GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into three groups and fed diets as described for the second experiment. The

animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg)was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. Teratology 53(2):p88, Abstract 21.

7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

7.9 Toxicodynamics, Toxico-Kinetics

Test Substance: [2-^{14}C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmole) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO [ ]

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid
Oral	***100 mg/kg*** (Repeated)	***12% glucuronide-2-Ethylhexanoic acid*** 12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid

		5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 **Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m^3 (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid

elimination of the material. No urine samples were collected during the work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be 2-2.33 x 10^{-4} mg/kilogram body weight/8 hour workday. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. Int. Arch. Occup. Environ. Health, 62:213-216.

9.0 **Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets**

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 **Availability and Reference(s) for Existing Review(s)**

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

Note: Appendix I is Robust Summaries and SIDS Dossier for 2-ethylhexanoic acid.

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, zinc salt
Chemical Name	:	Hexanoic acid, 2-ethyl, zinc salt
CAS Registry No.	:	136-53-8
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$C_{16}H_{30}O_4Zn$
Molecular Weight	:	351.8006
Synonyms and Trade names	:	Zinc 2-ethylhexanoate; ethylhexanoic acid zinc salt;
References	:	http://www.chemfinder.com

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Melting point is reported as –118.4°C for 2-ethylhexanoic acid (See Appendix I: 3.1)
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	> 350 °F
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Mixture of zinc 2-ethylhexanoate (98% by weight) and diethylene glycol monomethyl ether
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (See Appendix I.: 3.2)
Reliability	:	
Reference	:	MSDS dated 11/30/00, prepared by The Shepherd Chemical Company

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	1.17
Year	:	
GLP	:	
Test substance	:	Mixture of zinc 2-ethylhexanoate (98% by weight) and diethylene glycol monomethyl ether
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference		MSDS dated 11/30/00, prepared by The Shepherd Chemical Company

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value :
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Vapor pressure is reported as 1.33 x 10^{-3} kPa at 20°C for 2-ethylhexanoic acid (See Appendix I: 3.3)
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (See Appendix I: 3.4).
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : Negligible
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance : Mixture of zinc 2-ethylhexanoate (98% by weight) and diethylene glycol monomethyl ether
Deg. products CAS# :
Method :
Method detail :

Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The water solubility of 2-ethylhexanoic acid was reported to be 25 mg/L at 25°C (See Appendix I: 3.5).
Reliability	:	
Reference	:	MSDS dated 11/30/00, prepared by The Shepherd Chemical Company

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	> 250 °F
Year	:	
GLP	:	
Test substance	:	Mixture of zinc 2-ethylhexanoate (98% by weight) and diethylene glycol monomethyl ether
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** A flashpoint of 118°C was reported for 2-ethylhexanoic acid (See Appendix I: 3.6).
Reliability	:	
Reference	:	MSDS dated 11/30/00, prepared by The Shepherd Chemical Company

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	6.99 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Zinc 2-ethylhexanoate, 1% ethylene glycol monomethyl ether, CAS number 136-53-8, lot number F05L03, received from Alfa Aesar Chemical Company. Liquid, purity of 22.39% zinc.
Approximate water solubility	:	100 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of zinc 2-ethylhexanoate were prepared at a nominal concentration of 50 mg/L by fortification of degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.001N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKa value was 6.99 (SD = 0.0704) at 20°C

Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of zinc 2-ethylhexanoate, 1% ethylene glycol monomethyl ether, Wildlife International, Ltd. Study No. 534C-102, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	mg/l
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %

Control substance	:	
Kinetic	:	%
		%
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Aerobic biodegradation of 2-ethylhexanoic acid was reported with BOD_5, BOD_{10} and BOD_{20} at 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (See Appendix I: 5.1.1).
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
LC0 :
LC50 :
LC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The 96-h LC50 for fathead minnows (*Pimephales promelas*) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix I: 6.1.1).
Metal: The bioavailability and resultant aquatic toxicity of zinc is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. Reported 96-h LC50 values for zinc chloride (expressed as zinc) for various species of fish include 0.29 mg Zn/L and 0.42 mg Zn/L for bluegill (*Lepomis macrochirus*); 0.093 – 0.815 mg Zn/L for rainbow trout (*Oncorhynchus mykiss*); 0.45 - 2.25 mg Zn/L for common mirror-colored carp (*Cyprinus carpio*) and 1.70 mg Zn/L for sheepshead minnow (*Cyprinodon variegatus*) (ECOTOX database, 2002). The range of reported 96-h LC50 values (n = 15) for freshwater fish was 0.14 – 0.78 mg Zn/L for tests conducted with zinc chloride or zinc sulfate. (Risk Assessment for Zinc Metal, 2001, draft).
Reliability :
Reference :

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
EC0 :
EC50 :
EC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :

GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (See Appendix I: 6.2.1).
Metal: The bioavailability and resultant aquatic toxicity of zinc is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. Reported 48-h EC50 values for zinc chloride (expressed as zinc) for *Daphnia magna* include 0.33, 0.52, 0.66 and 0.80 mg Zn/L (ECOTOX database, 2002). For several crustaceans, including *Daphnia magna*, *Ceriodaphnia dubia*, and *Ceriodaphnia reticulata*, reported 48-h EC50 values ranged from 0.068 to 0.86 mg Zn/L, for zinc tested as zinc chloride or zinc sulfate. For *Daphnia magna*, reported EC50 values for zinc powder were 0.15 – 0.5 mg Zn/L . (Risk Assessment for Zinc Metal, 2001, draft).
Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The 96-h E_bC50 (EC50 based upon biomass) for the green alga *Scenedesmus subspicatus* was reported to be 40.616 mg/L for 2-ethylhexanoic acid (See Appendix I: 6.3).
Metal: The bioavailability and resultant aquatic toxicity of zinc is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. The reported 96-h EC50 for zinc chloride for the green alga *Selenastrum capricornutum* was 0.0447 mg Zn/L, while the reported 72-h EC50 for the marine diatom *Skeletonema costatum* was 0.142 mg Zn/L (ECOTOX database, 2002). For zinc powder, the reported 72-h EC50

value based upon growth rate for *Selenastrum capricornutum* was 0.150 mg Zn/L (Risk Assessment for Zinc Metal, 2001, draft).

Reliability :

Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:
Type	:
Guideline/method	:
Species	:
Number of animals	:
Males	:
Females	:
Doses	:
Males	:
Females	:
Vehicle	:
Route of administration	:
Exposure time	:
Product type guidance	:
Decision on results on acute tox. tests	:
Adverse effects on prolonged exposure	:
Half-lives	: 1st: 2nd: 3rd:
Toxic behavior	:
Deg. product	:
Deg. products CAS#	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and

1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid
		7% glucuronide-diacid or hydroxylated 2- Ethylhexanoic acid
		2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid
		14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid
		12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid
		3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid

		3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid
		9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Metal: Zinc is an essential element in nutrition, and is important in membrane stability, in over 300 enzymes, and in the metabolism of proteins and acids. (WHO, 2001, Environmental Health Criteria 221, Zinc). Absorption of zinc in laboratory animals can vary from 10-40% depending upon nutritional status and other ligands in the diet. Absorbed zinc is mainly deposited in muscle, bone, liver, pancreas, kidney and other organs. The biological half-life of zinc is about 4-50 days in rats, depending on the administered dose (WHO, 2001, Environmental Health Criteria 221, Zinc). . Increases in zinc concentration in the bodies of experimental animals exposed to zinc are accompanied by reduced levels of copper, suggesting that some of the signs of toxicity ascribed to zinc may be caused by zinc-induced copper deficiency. Moreover, studies have shown that exposure to zinc alters the levels of other essential metals, including iron. Zinc deficiency in animals is characterized by a reduction in growth and cell replication, adverse reproductive and developmental effects, and reduced immunoresponsiveness. (WHO, 2001, Environmental Health Criteria 221, Zinc).

Reliability :

Reference :

5.1.1 ACUTE ORAL TOXICITY

Type	:	Acute Oral (LD50) Toxicity
Guideline/Method	:	
Species	:	Rat
Strain	:	Sherman-Wistar albino
Sex	:	Male and female
Number of animals	:	10 per dose (5 male, 5 female)
Vehicle	:	
Doses	:	1.58, 2.0, 2.51, 3.16, 3.98, 5.01 and 6.32 g/kg
LD50	:	Males: 3.7 g/kg (95% CI: 3.04 – 4.62 g/kg). Females: 3.55 g/kg (95% CI: 2.95 – 4.26 g/kg)
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150. Described as zinc 2-ethylhexanoate 79.1%, mineral spirits 20.9% (CAS # 8032-32-4). Negligibly soluble in water, soluble in organic solvents. Density 1.022 g/mL.
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.
Method detail	:	Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation. Observed for 14-days post-exposure.

Result	:	LD50 for Males: 3.7 g/kg (95% CI: 3.04 – 4.62 g/kg). LD50 for Females: 3.55 g/kg (95% CI: 2.95 - 42.6 g/kg). For males: 3/5, 4/5 and 5/5 rats died at the three highest doses, respectively. One rat died at 2.51 g/kg and one rat died at 3.16 g/kg. For females: 2/5, 3/5, 5/5, and 5/5 rats died at the four highest doses, respectively. For both sexes, within 1-2 hr following dosing, animals displayed numerous symptoms (slight ataxia, depression, ruffled, and drooling at lower doses; semi-comatose and death higher doses). Animals, which survived, recovered fully after 1-4 days. Gross necropsies were unremarkable.
Remark	:	**Supporting data for dissociation products:** **Acid:** The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (See Appendix I: 7.1.1). **Metal:** Acute oral toxicity in rodents exposed to zinc is low, and the level at which zinc produces no adverse effect in rats is approximately 160 mg/kg body weight (WHO, 2001, Environmental Health Criteria 221, Zinc). Of the compounds zinc nitrate, zinc sulfate, zinc chloride and zinc acetate, zinc acetate was the most toxic, with oral LD50 values of 237 mg Zn/kg bw (rat) and 86 mg Zn/kg bw (mouse). The LD50 for zinc chloride in an oral exposure was reported to be 528 mg Zn/kg bw in rats and 605 mg Zn/kg bw in mice (ATSDR, 1994, Toxicological Profile for Zinc).
Reliability	:	[2] Reliable with restrictions. Basic data provided, exposure conditions not fully described. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), study conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	Limit Test
Guideline/method	:	
Species	:	Rat
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	10 (5 male and 5 female)
Vehicle	:	
Doses	:	One concentration, 23.2 mg/L of a 25% w/v suspension in mineral spirits. Median particle diameter measured to ensure a respirable dose was received.
Exposure time	:	1 hour
LC50	:	> 23.2 mg/L (maximum attainable nominal concentration)
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate 18% (Lot # 150), prepared and used as a 25% w/v suspension in mineral spirits.
Method	:	
Method detail	:	Animals (205 – 210 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 70ºF. Test material concentration was measured and determined to be 23.2 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 1.1 microns MMD (mass median diameter). Animals observed for 14 days post-exposure
Result	:	No mortality, no toxicity, and no adverse gross necropsy findings

Remark	:	**Supporting data for dissociation products:** **Acid:** The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (See Appendix I: 7.1.2). **Metal:** Zinc chloride is a primary ingredient in smoke bombs, resulting in respiratory injury. In a 10-minute inhalation study with rats, zinc chloride aerosol was lethal at concentrations as low as 940 mg Zn/m3 (Risk Assessment for Zinc Metal, 2001, draft).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Exposure conditions not described, duration of exposure and determination of measured test concentrations less than current guidelines require.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.3 ACUTE DERMAL TOXICITY

Type	:	Limit Test
Guideline/method	:	
Species	:	Rabbit
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	Six (3 male and 3 female)
Vehicle	:	
Doses	:	One dose, 5 g/kg
LD50	:	> 5 g/kg
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150. Described as zinc 2-ethylhexanoate 79.1%, mineral spirits 20.9% (CAS # 8032-32-4). Negligibly soluble in water, soluble in organic solvents
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.40.
Method detail	:	Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious damming. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure.
Result	:	No mortality or toxicity. No adverse gross necropsy findings
Remark	:	**Supporting data for dissociation products:** **Acid:** The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted) was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg.(See Appendix I: 7.1.3). **Metal:** Zinc chloride is reported to cause moderate to severe skin irritation in the rabbit, guinea pig and mouse at 0.48 mg Zn/cm2 while zinc acetate at 7.2 mg Zn/cm2 was reported to be irritating to the rabbit and mouse but caused no effects in the guinea pig (ATSDR, 1994, Toxicological Profile for Zinc)..
Reliability	:	[2] Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.1 SKIN IRRITATION

Type	:	Contact dermal irritation/sensitization
Guideline/method	:	
Species	:	Guinea pig, albino
Strain	:	
Sex	:	Male, weighing 300 – 400 g
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	10
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150.
Method	:	
Method detail	:	A 0.5 mL portion of material was applied to the intact skin test sites on the guinea pigs. A gauze patch was placed over the treated area and an impervious material was wrapped snugly around the trunks of the animals to hold the patch in place. After 24 hours, the patch was removed, the animals allowed to rest for 1 day, and another application was made to the same skin site. This sequence was repeated for a total of 10 applications, after which time the animals were given a two week rest period. Subsequently a challenge application was put on skin sites differing from the original test sites. The challenge application remained on for 24 hours. The sites were examined for irritation using the Draize method of scoring, 24 hours after each induction application and 24 and 48 hours after the challenge application.
Result	:	The test substance was a primary skin irritant and a fatiguing agent, but not a sensitizing agent.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1 (B)). **Metal:** Zinc chloride, applied daily as a 1% aqueous solution in an open patch test for 5 days, was severely irritant in rabbits, guinea pigs and mice, inducing epidermal hyperplasia and ulceration. Aqueous zinc acetate (20%) was slightly less irritant. (WHO, 2001, Environmental Health Criteria 221, Zinc).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.2 EYE IRRITATION

Type	:	Primary eye irritation
Guideline/method	:	
Species	:	Rabbits, young adults
Strain	:	Albino
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	Six

Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zinc octoate, 18%, Lot # 150.
Method	:	
Method detail	:	0.1 mL of the test material was instilled into the right eyes of the animals while the other eye served as the untreated control. The test material was not washed from the eyes. The treated eyes were examined at 1, 2, 3, 5, and 7 days following exposure. Results were scored according to the Draize Scale of Scoring Ocular Lesions.
Result	:	The test substance was not a primary ocular irritant within the definition of the Federal Hazardous Substances Act.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours (See Appendix I: 7.2.2; note study is of low reliability). **Metal:** no data
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	
Control group	:	
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery. Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups

consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Appendix I: 7.4(H)). These data are consistent with four previous repeated dose studies in Fischer rats (See Appendix I: 7.4).

Metal: Long-term oral exposure to zinc indicates the target organs of toxicity to be the hematopoeitic system in rats, ferrets and rabbits; the kidney in rats and ferrets; and the pancreas in mice and ferrets (WHO, 2001, Environmental Health Criteria 221, Zinc). The daily oral administration of zinc chloride to rats in water over a 4 week period produced a LOAEL of 12 mg Zn/kg/d, based upon hematological effects. Zinc acetate given to rats in water over three months yielded NOAEL values of 95 to 191 mg Zn/kg/d. During a 13-week exposure to zinc sulfate via the diet, NOAEL values for the rat ranged from 53 to 565 mg Zn/kg/day and for the mouse were 104 mg Zn/kg/d, based upon various parameters. (ATSDR, 1994, Toxicological Profile for Zinc).

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Mutagenicity
Guideline/method :
System of testing : Ames assay, standard plate assay

Species	:	*Salmonella typhimurium*
Strain	:	TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations	:	1, 10, 100, 500, and 1000 µg/plate, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254 per Ames et al., 1975, Mut. Res. 31:347-364. No further details.
Year	:	1980
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Zinc octoate 18%, Lot No. 150
Method	:	Followed method of Ames et. al.
Method detail	:	0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37ºC and number of colonies compared to background. No further details provided.
Result	:	Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of *S. typhimurium* tested, either with or without activation. Mutagenic index of all five strains was less than 2.0. Positive controls produced the expected response.
Remark	:	**Supporting data for dissociation products:** **Acid:** In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid either with or without activation (See Appendix I: 7.5.1). **Metal:** In 11 separate *in vitro* studies with zinc chloride or zinc sulfate, negative results were reported with the exception of two ambiguous results and one weakly positive result. (Risk Assessment for Zinc Metal, 2001, draft).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Van Goethem, D., 1980. Evaluation of zinc octoate in the *Salmonella*/Microsome (Ames) assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Bacterial DNA damage or repair assay
Species	:	*Escherichia coli*
Strain	:	W3110 (pol A^+) and its DNA polymerase deficient derivative p3478 (pol A^-)
Test concentrations	:	5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in DMSO.
Cytotoxic concentr.	:	
Metabolic activation	:	With and without. Activation with S-9 from Aroclor 1254 induced rat liver per Ames al., 1975, Mut. Res. 31:347-364 .
Year	:	1981
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Zinc octoate 18%, Lot No. 150
Method	:	Followed method of Rosenkranz et al. (1971).
Method detail	:	Test material (5 concentrations) applied to cells in culture. Vehicle controls (DMSO) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 ug/mL without activation and 2-aminofluorene at 200 ug/mL with activation). Bacteria (10^4) of each strain were exposed to the test material for 1 hour at 37ºC. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37ºC and the number of viable cells determined.

Result : Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A^- to pol A^+ survivors), with or without activation. Survival index at all nonprecipitating dose levels was greaten than 0.80. Noted that two highest concentrations (with and without activation) caused a white precipitate to form, hence data from these concentrations not useful.

Remark :

Reliability : [2] Reliable with restrictions. Basic data provided. Comparable to guideline.

Reference : Van Goethem, D., 1981. Evaluation of zinc octoate, 18%, in the *E. coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

5.6 GENETIC TOXICITY 'IN VIVO'

Type :

Guideline/method :

Species :

Strain :

Sex :

Route of admin. :

Exposure period :

Doses :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (See Appendix I: 7.5.3).
Metal: Studies on the induction of chromosome aberrations in bone marrow cells harvested from animals exposed to zinc yield equivocal and sometimes contradictory results. Increased aberrations have been seen in rats after oral exposure to zinc chloride in water (249 mg/L for 14 days) and in mice administered intraperitoneal injections of zinc chloride (2-5 mg/kg as zinc chloride). In contrast, other studies have produced negative findings or have suggested that the induction of aberrations is contingent upon concomitant calcium deficiency. Negative results have been reported in the mouse micronucleus test (i.p. injection of zinc sulfate) and in the dominant lethal mutation assay with mice (i.p. injection of zinc chloride at 15 mg/kg). (WHO, 2001, Environmental Health Criteria 221, Zinc).

Reliability :

Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :

Guideline/method :

Species :

Strain :

Sex :

Route of admin. :

Exposure period :

Frequency of treatment :

Duration of test :

Doses	:
Control group	:
NOAEL maternal tox.	:
NOAEL teratogen.	:
Other	:
Other	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (See Appendix I: 7.7.2). In the most reliable study, the NOEL for teratogenic and developmental effects in rats for was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight were noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters was significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(See Appendix I: 7.2.2 (E and F))

Metal: Second-generation mice (from mothers fed zinc carbonate) exposed to high doses of zinc throughout the gestation, lactation, and postweaning period had elevated levels of zinc in their bones, decreased blood copper levels, lowered hematocrit values and reduced body weights. The offspring of pregnant rats fed zinc carbonate (500 mg Zn/kg) did not demonstrate any

pregnant rats fed zinc carbonate (500 mg Zn/kg) did not demonstrate any increase in the incidence of malformations. (WHO, 2001, Environmental Health Criteria 221, Zinc). Several developmental toxicity studies were conducted with zinc sulfate on mice, rats, hamsters and rabbits, in general accordance with OECD Guideline 414; however the form of the zinc sulfate was not specified. Depending upon the form that was used, the calculated NOAEL values ranged from 6.8 mg Zn/kg bw for the mouse to 35.2 mg Zn/kg bw for the hamster. (Risk Assessment for Zinc Metal, 2001, draft).

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:
Acid: A One-Generation Reproduction Toxicity Study was conducted with 2-ethylhexanoic acid. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in

sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

(See Appendix I: 7.7.1)

Metal: Rats fed zinc chloride daily over an 8 week period demonstrated altered sperm chromatin structure with a LOAEL of 25 mg Zn/kg/d. The LOAEL for serious reproductive effects in female rats was 200 and 250 mg Zn/kg/d from exposure to zinc sulfate and zinc carbonate, respectively, in the diet. (ATSDR, 1994, Toxicological Profile for Zinc).

Reliability :
Reference :

12.0 OTHER INFORMATION

6.1. CARCINOGENICITY

No evidence has shown that zinc salts administered orally or parenterally are tumorigenic. (WHO, 2001, Environmental Health Criteria 221, Zinc).

APPENDIX I

ROBUST SUMMARIES and

SIDS DOSSIER for:
2-Ethylhexanoic Acid

••••••••••••••••••••

CAS No. 149-57-5

Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

		Page
SIDS PROFILE		1
SIDS SUMMARY		2
1.0	GENERAL INFORMATION	4
2.0	CHEMICAL IDENTITY	4
	*2.1 CAS NUMBER	4
	*2.2 NAME	4
	2.3 COMMON SYNONYMS	4
	2.4 EMPIRICAL FORMULA	5
	*2.5 STRUCTURAL FORMULA	5
	2.6 PURITY OF INDUSTRIAL PRODUCT	5
	2.6.1 DEGREE OF PURITY	5
	2.6.2 IDENTITY OF MAJOR IMPURITIES	5
	2.6.3 ESSENTIAL ADDITIVES	5
3.0	PHYSICAL-CHEMICAL DATA	5
	*3.1 MELTING OR DECOMPOSITION POINT	5
	*3.2 BOILING POINT	5
	*3.3 VAPOR PRESSURE	6
	*3.4 PARTITION COEFFICIENT N-OCTANOL/WATER	6
	*3.5 WATER SOLUBILITY	7
	3.6 FLASH POINT (LIQUIDS)	7
	3.7 FLAMMABILITY	7
	3.8 PH IN WATER	8
	3.9 OTHER DATA	8
4.0	SOURCE OF EXPOSURE	8
	*4.1 PRODUCTION LEVELS EXPRESSED AS TONNES PER ANNUM	8
	4.2 PROCESSES	8
	*4.3 INFORMATION CONCERNING USES	8
	4.4 OPTIONS FOR DISPOSAL	8
	4.5 OTHER REMARKS	9
5.0	ENVIRONMENTAL FATE AND PATHWAYS	9
	5.1 DEGRADABILITY (BIOTIC AND ABIOTIC)	9
	5.1.1 BIODEGRADABILITY	9
	5.1.2 SEWAGE TREATMENT	10
	5.1.3 STABILITY IN AIR	10
	5.1.4 STABILITY IN WATER	10
	5.1.5 IDENTIFICATIN OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE	10
	5.2 BIOACCUMULATION	11
	5.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS	11
	5.4 MONITORING DATA	11
6.0	ECOTOXICOLOGICAL DATA	11
	6.1 TOXICITY TO FISH	11
	6.1.1 RESULTS OF ACUTE TESTS	11
	6.1.2 RESULTS OF LONG-TERM TESTS	12
	6.2 TOXICITY TO DAPHNIDS	13
	6.2.1 RESULTS OF ACUTE TESTS	13
	6.2.2 RESULTS OF LONG-TERM TESTS	13
	6.3 TOXICITY TO ALGAE	14
	6.4 TOXICITY TO OTHER AQUATIC ORGANISMS	14

Page

6.5 TOXICITY TO BACTERIA 15
*6.6 TOXICITY TO TERRESTRIAL ORGANISMS 15
6.6.1 TOXICITY TO SOIL DWELLING ORGANISMS 15
6.6.2 TOXICITY TO PLANTS 15
6.6.3 TOXICITY TO BIRDS 15
6.7 BIOLOGICAL EFFECTS MONITORING 15
6.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES 15
7.0 TOXICOLOGICAL DATA 15
7.1 ACUTE TOXICITY 15
7.1.1 ACUTE ORAL TOXICITY 16
7.1.2 ACUTE INHALATION TOXICITY 17
7.1.3 ACUTE DERMAL TOXICITY 18
7.2 CORROSIVENESS/IRRITATION 19
7.2.1 SKIN IRRITATION 19
7.2.2 EYE IRRITATION 20
7.3 SKIN SENSITISATION 20
*7.4 REPEATED DOSE TOXICITY 21
*7.5 GENETIC TOXICITY 27
7.5.1 BACTERIAL TEST 27
7.5.2 NON-BACTERIAL IN VITRO TEST 28
7.5.3 NON-BACTERIAL TEST IN VIVO 29
7.6 CARCINOGENICITY 29
*7.7 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY 30
7.7.1 REPRODUCTIVE TOXICITY 30
7.7.2 TERATOGENICITY/DEVELOPMENTAL TOXICITY 32
7.8 SPECIFIC TOXICITIES (NEUROTOXICITY, IMMUNOTOXICITY, ETC.) 41
7.9 TOXICODYNAMICS, TOXICO-KINETICS 41
8.0 EXPERIENCE WITH HUMAN EXPOSURE 43
8.1 BIOLOGICAL MONITORING 43
9.0 RECOMMENDED PRECAUTIONS, CLASSIFICATION, AND SAFETY DATA 44
10.0 AVAILABILITY AND REFERENCE(S) FOR EXISTING REVIEW(S) 44

APPENDIX A 45

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH(CH_2\text{-}CH_3)\text{-}C(=O)\text{-}OH$
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5 STUDY	Info. Available Y/N	OECD Study Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degrability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5 STUDY	Info Available Y/N	OECD Summary Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

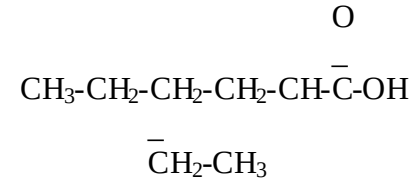
2.3 **Common Synonyms:**

a-Ethylcaproic acid
2-Ethylcaproic acid
a-Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**

$C_8H_{16}O_2$

* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **<u>Physical-Chemical Data</u>**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33×10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]

NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water** (Preferred Study)

log Pow = 3 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup [ ] open cup [X]

Method:

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 **pH in Water**

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES [ ]
NO [X]

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 **Other Data**

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 **Source of Exposure**

* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 **Other Remarks:**

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 **Environmental Fate and Pathways**

* 5.1 **Degradability (Biotic and Abiotic)**

5.1.1 **Biodegradability**

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic [ ]

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, J. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES [ ]
NO [X]

Test Results: BOD_5 = 60 % of Theoretical (2.44 g O_2/g test substance).
BOD_{10} = 76 % of Theoretical (2.44 g O_2/g test substance).
BOD_{20} = 83 % of Theoretical (2.44 g O_2/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 **Sewage Treatment**

Comments: No Data Available.

5.1.3 **Stability in Air** (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES [ ]

NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 **Stability in Water** (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES [ ]
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 **Identification of Main Mode of Degradability in Actual Use**

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES [ ]
NO [X]

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 **Ecotoxicological Data**

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static [X], semi-static [ ], flow-through [ ]
Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test Results: LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Daphnia magna (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES [ ]
NO [X]

Test Results: 48 hr EC_{50} = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC_0 = 62.5 mg/L, 48 hr EC_{100} = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC_0 - highest tested concentration without effect after 48 hours. EC_{100} - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengessellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES [ ]
NO [X]

Test Results: 72 hr EbC_{10} = 32.543 mg/L
72 hr EbC_{50} = 60.511 mg/L

96 hr EbC_{10} = 24.496 mg/L
96 hr EbC_{50} = 40.616 mg/L

72 hr EuC_{10} = 31.940 mg/L
72 hr EuC_{50} = 49.279 mg/L

96 hr EuC_{10} = 27.938 mg/L
96 hr EuC_{50} = 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

6.5 **Toxicity to Bacteria**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.6 **Toxicity to Terrestrial Organisms**

6.6.1 **Toxicity to Soil Dwelling Organisms**

Test Results: No Data Available.

6.6.2 **Toxicity to Plants**

Test Results: No Data Available.

6.6.3 **Toxicity to Birds**

Test Results: No Data Available.

6.7 **Biological Effects Monitoring (Including Biomagnification)**

Test Results: No Data Available.

6.8 **Biotransformation and Kinetics in Environmental Species**

No Data Available.

7.0 **Toxicological Data** (oral, dermal and inhalation, as appropriate)

* 7.1 **Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES [ ]
NO [X]

Test Results: Discriminating dose (for fixed dose only): LD_{50} = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES [X]
NO [ ]

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 Acute Dermal Toxicity

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES [ ]
NO [X]

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance**: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES [X]
NO [ ]

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 Eye Irritation

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES [ ]

NO [X]

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

7.3 Skin Sensitisation

Test Substance:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES [ ]
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES [ ]
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. Toxicol. Lett. 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed

consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized in extremis. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]

NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-dose groups, respectively. One male from the mid-dose group was found dead during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights

only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and mid-dose groups. Absolute and relative (to body weight) liver weight were significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly

higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of

female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 Genetic Toxicity

7.5.1 Bacterial test

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: S. typhimurium TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES [ ]

NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]

without metabolic activation: [ ] [ ] [X]

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES [ ]

NO [ ]

Test Results: No Data Available.

Comments:

Reference:

7.5.3 **Non-Bacterial Test *In Vivo***

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

GLP: YES [X]
NO [ ]

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

Comments: 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. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 **Carcinogenicity**

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]
NO [X]

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were

slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early

fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and Postnatal Development in Wistar Rats. Fundam. Appl. Toxicol. in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [ ]
NO [X]

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethyhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratol. 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES [ ]
NO [X]

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryolethality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryolethality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. Life Sci. 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES [ ]
NO [X]

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs was significantly higher in

the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in .the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. Fundam. Appl. Toxicol. 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrlBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour preiod; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

GLP: YES [ ]
NO [X]

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage of resorptions increased at higher dose levels, and was also high in the

animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs

of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. Toxicol. Appl. Pharmacol. 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]

NO [ ]

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(G.) **Teratogenicity/Developmental toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days

(GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into three groups and fed diets as described for the second experiment. The animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg)was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. Teratology 53(2):p88, Abstract 21.

7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

7.9 Toxicodynamics, Toxico-Kinetics

Test Substance: [2-^{14}C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmole) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO [ ]

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid

Oral	***100 mg/kg***	***12% glucuronide-2-Ethylhexanoic acid***
	(Repeated)	12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 **Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m^3 (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5

ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid elimination of the material. No urine samples were collected during the work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be 2-2.33 x 10^{-4} mg/kilogram body weight/8 hour workday. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. Int. Arch. Occup. Environ. Health, 62:213-216.

9.0 Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 Availability and Reference(s) for Existing Review(s)

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

Note: Appendix I is Robust Summaries and SIDS Dossier for 2-ethylhexanoic acid.

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, zirconium salt
Chemical Name	:	Hexanoic acid, 2-ethyl, zirconium salt
CAS Registry No.	:	22464-99-9
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$C_{16}H_{30}O_5Zr$
Molecular Weight	:	393.63
Synonyms and Tradenames	:	Zirconium 2-ethylhexanoate; Zirconium octoate; Zirconyl 2-ethylhexanoate; Zirconium versalate liquid, 24%
References	:	http://www.chemfinder.com; MSDS prepared by The Shepherd Chemical Company, dated 5/15/01.

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Melting point is reported as –118.4°C for 2-ethylhexanoic acid (See Appendix I: 3.1)
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	> 300 °F (relative to mineral spirits)
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (See Appendix I.: 3.2)
Reliability	:	
Reference	:	MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	1.28
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference		MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	2.0 mm Hg (relative to mineral spirits)
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Vapor pressure is reported as 1.33 x 10^{-3} kPa at 20°C for 2-ethylhexanoic acid (See Appendix I: 3.3)
Reliability	:	
Reference	:	MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (See Appendix I: 3.4).
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	Negligible
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Deg. products CAS#	:	
Method	:	

Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The water solubility of 2-ethylhexanoic acid was reported to be 25 mg/L at 25°C (See Appendix I: 3.5).
Reliability	:	
Reference	:	MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	106 °F (PMcc)
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Method	:	Closed cup
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** A flashpoint of 118°C was reported for 2-ethylhexanoic acid (See Appendix I: 3.6).
Reliability	:	
Reference	:	MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	5.81, 7.09. 7.65, and 8.24 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Zirconium (IV) 2-ethylhexanoate, lot number 119L09, received from Alfa Aesar Chemical Company. Liquid, purity of 18.17% ZrO2.
Approximate water solubility	:	50 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of zirconium(IV) 2-ethylhexanoate were prepared at a nominal concentration of 25 mg/L by fortification of degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in tetrahydrofuran. Each sample was titrated against 0.001N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the first equivalence point and thereafter, a minimum of three incremental additions were made before each of the three remaining equivalence points. The titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 3 points for each equivalence point on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.

Result	:	Mean (N = 3) pKa values were 5.81 (SD = 0.0806), 7.09 (SD = 0.0491), 7.65 (SD = 0.0689), and 8.24 (SD = 0.0299) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of zirconium (IV) 2-ethylhexanoate, Wildlife International, Ltd. Study No. 534C-104, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	mg/l
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % %

%

Control substance :

Kinetic : %

%

Deg. product :

Year :

GLP :

Test substance :

Deg. products CAS# :

Method :

Method detail :

Result :

Remark : **Supporting data for dissociation products:**
Acid: Aerobic biodegradation of 2-ethylhexanoic acid was reported with BOD_5, BOD_{10} and BOD_{20} at 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (See Appendix I: 5.1.1).

Reliability :

Reference :

3.7 BIOCONCENTRATION

Type :

Guideline/method :

Species :

Exposure period : at °C

Concentration :

BCF :

Elimination :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark :

Reliability :

Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	Acute toxicity to fish. Static exposure.
Guideline/method	:	
Species	:	*Lepomis macrochirus* (bluegill sunfish, freshwater)
Exposure period	:	96 hours
NOEC	:	
LC0	:	
LC50	:	LC50 greater than tested concentration (100% of a 24% zirconium octoate solution).
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	:	Test concentrations were control and 100% concentration of a 24% zirconium octoate solution. Test conducted in reconstituted freshwater (hardness = soft water) and temperature range of 19 – 22.5ºC. Fish were < 1 year old and of same age class. Biological loading was 0.3 g/L.
Result	:	No mortality observed in 100% concentration of a 24% calcium octoate solution.
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h LC50 for fathead minnows (*Pimephales promelas*) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix I: 6.1.1). **Metal:** For zirconium tetrachloride, the 96-h LC50 for rainbow trout (*Oncorhynchus mykiss*) was reported to be greater than 20 mg Zr/L; for the zirconium salt of sulfuric acid, the 96-h LC50 for *Pimephales promelas* was reported to be 14 – 145 mg Zr/L; for zirconium oxychloride, the 96-h LC50 for *Lepomis macrochirus* was reported to be 15 – 270 mg Zr/L and for *Pimephales promelas*, 18 –240 mg Zr/L. (ECOTOX database, 2002).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished, and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

Type	:	Acute toxicity to fish. Static exposure.
Guideline/method	:	
Species	:	*Cyprinodon variegatus* (sheepshead minnow, saltwater)
Exposure period	:	96 hours
NOEC	:	
LC0	:	

LC50	:	LC50 greater than tested concentration (100% of a 24% zirconium octoate solution).
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	:	Test concentrations were control and 100% concentration of a 24% zirconium octoate solution. Test conducted using synthetic seawater (28 ppt), temperature range of 20 - 22ºC, fish < 1 yr old and of same age class, biological loading 0.9 g/L.
Result	:	No mortality observed in 100% concentration of a 24% calcium octoate solution.
Remark	:	
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished, and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Acute toxicity to daphnids. Static exposure.
Guideline/method	:	
Species	:	*Daphnia magna*
Exposure period	:	48 hours
NOEC	:	
EC0	:	
EC50	:	48-h EC50: 58.1% (95% CI: 46 - 73.3%)
EC100	:	
Other	:	24-h EC50 could not be estimated because of insufficient mortality
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Daphnia, 365-0
Method detail	:	Test conducted in filtered (0.22 µ) lake water (hardness = soft), temperature range 19 - 21ºC. Test concentrations were 0, 10, 18, 32, 56 and 100% of zirconium octoate (24% solution). No information on test organisms.

		zirconium octoate (24% solution). No information on test organisms.
Result	:	48-h EC50: 58.1% (95% CI: 46 – 73.3%); 24-h EC50: could not be calculated because of low mortality
Remark	:	**Supporting data for dissociation products:** **Acid:** The 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (See Appendix I: 6.2.1). **Metal:** For zirconium chloride, the 3-week LC50 for *Daphnia magna* was reported to be 2 mg Zr/L (ECOTOX database, 2002).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	Algal acute toxicity test
Guideline/method	:	
Species	:	*Selenastrum capricornutum* (freshwater green alga)
Endpoint	:	„growth“ (not specified further; could be growth rate, yield or viability)
Exposure period	:	96 hours
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	0.07%
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Algae, 357-0
Method detail	:	Test concentrations were 0, 0.6, 0.10, 0.18, 0.32 and 0.56%. Stock solution prepared by adding an excessive amount of zirconium octoate (24%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used freshwater algal maintenance medium and test temperature 19 - 20ºC.
Result	:	96-h EC50 was 0.07%
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h E_bC50 (EC50 based upon biomass) for the green alga *Scenedesmus subspicatus* was reported to be 40.616 mg/L for 2-ethylhexanoic acid (See Appendix I: 6.3). **Metal:** For zirconium tetrachloride, the 96-h EC50 for *Selenastrum capricornutum* was reported to be 2.6 mg Zr/L (ECOTOX database, 2002).

capricornutum was reported to be 2.6 mg Zr/L (ECOTOX database, 2002).

Reliability : [3] Not reliable. Test material inadequately described and reported to be not soluble in water. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Non-standard test conditions, lack of detail on methods. Secondary reference.

Reference : Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

Type : Algal acute toxicity test
Guideline/method :
Species : *Skeletonema costatum* (saltwater diatom)
Endpoint : „growth“ (not specified further; could be growth rate, yield or viability)
Exposure period : 96 hours
NOEC :
LOEC :
EC0 :
EC10 :
EC50 : 0.08%
Other :
Other :
Other :
Limit test :
Analytical monitoring : None reported
Year : 1981
GLP : Not reported
Test substance : Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method : United States Testing Company protocol PRO/FT, Algae, 357-0
Method detail : Test concentrations were 0, 0.6, 0.10, 0.18, 0.32 and 0.56%. Stock solution prepared by adding an excessive amount of zirconium octoate (24%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used seawater algal medium I and test temperature 19 - 20ºC
Result : 96-h EC50 was 0.08%
Remark :
Reliability : [3] Not reliable. Test material inadequately described and reported to be not soluble in water. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Non-standard test conditions, lack of detail on methods. Secondary reference.
Reference : Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.4 ACUTE TOXICITY TO AVIAN SPECIES

Type : Limit test

Guideline/method	:	
Species	:	Bobwhite quail (*Colinus virginianus*)
Number, sex and age of animals	:	22 birds (11 males and 11 females), approximately 16 weeks old (200 ± 30 g)
Exposure period	:	14 days
NOEL	:	
LD50	:	> 2000 mg/kg
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	No
Test substance	:	Zirconium octoate, administered as a 20% w/v suspension in corn oil
Method	:	
Method detail	:	Birds were housed in metal cages with wire floors, under a photoperiod of 17 hours light and 7 hours dark, mean humidity of 71% and mean temperature of 20°C (range 14 - 28°C). Birds were provided with water and standard diet ad libitum (except overnight starvation prior to dosing). Dose levels included vehicle control and 2000 mg/kg, administered by oral gavage. Mortalities were recorded daily. Body weights were recorded prior to dosing and at days 3, 7 and 14. Food consumption was recorded weekly. All birds were examined at death or test termination for gross pathology.
Result	:	Following dosing, birds dosed with zirconium octoate were quiet and subdued, but recovered after 19 hours and remained in good health for the rest of the study. Body weight changes were considered to be within normal limits. Food consumption was similar in the dosed birds and the controls. No abnormalities were detected in any birds.
Remark	:	
Reliability	:	[3] Not reliable. Test material inadequately described. Secondary reference.
Reference	:	Previously abstracted information from studies conducted by Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. Original study report not available.

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:
Type	:
Guideline/method	:
Species	:
Number of animals	:
Males	:
Females	:
Doses	:
Males	:
Females	:
Vehicle	:
Route of administration	:
Exposure time	:
Product type guidance	:
Decision on results on acute tox. tests	:
Adverse effects on prolonged exposure	:
Half-lives	: 1st: 2nd: 3rd:
Toxic behavior	:
Deg. product	:
Deg. products CAS#	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and

1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid
		7% glucuronide-diacid or hydroxylated 2- Ethylhexanoic acid
		2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid
		14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid
		12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid
		3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid

		3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid
		9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Metal: Zirconium salts when parenterally administered are slowly absorbed from injection sites and simple cationic salts cause local irritation. Intravenously injected cationic salts form insoluble colloidal polymers and are phagocytized by macrophages. Young rats absorb more parenterally injected zirconium salts than adult or old animals, and young rats retain them longer in their skeleton because of vigorous metabolism in bone marrow. Excretion is mainly through feces, owing to poor alimentary absorption of orally-ingested zirconium salts and to the accumulation of soluble zirconium salts in the liver with their subsequent return to the alimentary tract by the bile. Less than 1% of the daily intake of zirconium of humans is excreted in urine. Absorbed zirconium is either sequestered in the skeleton or excreted very rapidly. A mechanism of zirconium homeostasis is apparently present in humans. (Hazardous Substances Data Bank, online at , subsequently referred to as HSDB, 2002). The biochemical properties of zirconium include a high affinity for phosphate groups and an inhibitory effect on many enzymes (Couture, P., C. Blaise, D. Cluis and C. Bastien, 1989, Zirconium toxicity assessment using bacteria, algae and fish assays, Water, Air and Soil Pollut. 47: 87-100)..

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type : Limit Test
Guideline/Method :
Species : Rat
Strain : Sherman-Wistar albino
Sex : Male and female
Number of animals : 10 (5 male, 5 female)
Vehicle :
Doses : 5.0 g/kg
LD50 : >5.0 g/kg for both males and females.
Year : 1980
GLP : Not reported
Test substance : Zirconium octoate, 24%, Lot # 28702. Density approx. 1.3 g/mL.
Method : Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.
Method detail : Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation. Observed for 14-days post-exposure.
Result : No mortality observed. LD50 for both sexes > 5.0 g/kg For both sexes, within 1 hr following dosing, animals were slightly ataxic, depressed, ruffled, and drooling. After 2-3 hours they were semi-comatose to comatose. They remained severely depressed, ruffled, drooling and dirty for 2-3 days before

		beginning to recover. After 5 days the animals appeared essentially normal. Gross necropsies were unremarkable.
Remark	:	**Supporting data for dissociation products:** **Acid:** The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (See Appendix I: 7.1.1). **Metal:** Zirconium salts have low oral toxicity; both the tetrachloride and oxychloride are poorly adsorbed and therefore have low oral toxicities with LD50 values in the rat of 0.7 g/kg and 3.5 g/kg, respectively. Toxicity is increased by intraperitoneal injection (LC50 of 400 mg/kg in rats for zirconium oxychloride). (HSDB, 2002)
Reliability	:	[2] Reliable with restrictions. Basic data provided, exposure conditions not fully described, test material not described. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), study conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	Limit Test
Guideline/method	:	
Species	:	Rat
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	10 (5 male and 5 female)
Vehicle	:	
Doses	:	One concentration, 8.8 mg/L of a 50% w/v suspension in mineral spirits. Median particle diameter measured to ensure a respirable dose was received.
Exposure time	:	1 hour
LC50	:	> 8.8 mg/L (maximum attainable nominal concentration)
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate 24% (Lot # 28702), prepared and used as a 50% w/v suspension in mineral spirits.
Method	:	
Method detail	:	Animals (200 – 210 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 70ºF. Test material concentration was measured and determined to be 8.8 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 0.68 microns MMD (mass median diameter). Animals observed for 14 days post-exposure
Result	:	No adverse effects were observed during the exposure period or during the two-week post exposure period. No mortality, no toxicity, and no adverse gross necropsy findings
Remark	:	**Supporting data for dissociation products:** **Acid:** The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (See Appendix I: 7.1.2). **Metal:** Severe, persistent interstitial pneumonitis has been produced in experimental animals exposed to airborne zirconium concentrations of 5 mg/m3 (HSDB, 2002).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Exposure conditions not described, duration of exposure and determination of measured test concentrations less than current guidelines require.

concentrations less than current guidelines require.

Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.3 ACUTE DERMAL TOXICITY

Type : Limit Test
Guideline/method :
Species : Rabbit
Strain : Albino
Sex : Male and female
Number of animals : Six (3 male and 3 female)
Vehicle :
Doses : One dose, 5 g/kg
LD50 : > 5 g/kg
Year : 1980
GLP : Not reported
Test substance : Zirconium octoate, 24%, Lot # 28702. Density approx. 1.3 g/mL.
Method : Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.40.
Method detail : Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious damming. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure. Gross autopsies conducted on all dead and surviving animals.
Result : No mortality or toxicity. No adverse gross necropsy findings in this limit test.
Remark : **Supporting data for dissociation products:**
Acid: The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted) was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg.(See Appendix I: 7.1.3)
Metal: No data
Reliability : [2] Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.
Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.1 SKIN IRRITATION

Type : Primary skin irritation
Guideline/method :
Species : Rabbit, albino
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals : Six
Vehicle :
Classification : Not classified as a primary skin irritant

Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate, 24%, Lot # 28702
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.41.
Method detail	:	Rabbits were clipped over a wide area. One side of the animals' backs was abraded at one site with a lancet sufficiently deep to penetrate the stratum corneum but not enter the derma to produce bleeding. A 0.5 mL portion of the test material was applied to an abraded and an intact skin site on the same animal. The treated areas were covered with gauze patches and an impervious material was wrapped around the trunks to hold the patches in place. After 24 hours, the wrapping was removed and the treated areas examined. Readings were also made after 72 hours. The Draize method of scoring was used.
Result	:	The test substance was not a primary skin irritant to rabbits within the definition of the Federal Hazardous Substances Act. The primary irritation score was 0.96.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1 (B)) **Metal:** Certain zirconium salts (e.g. zirconium tetrachloride) may cause irritation or caustic injury. Dermal exposure to zirconium in topical poison ivy medications and deodorants has caused subcutaneous granulomas, probably due to a hypersensitivity reaction. (HSDB, 2002).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

Type	:	Contact dermal irritation/sensitization
Guideline/method	:	
Species	:	Guinea pig
Strain	:	
Sex	:	Male, weighing 300 – 400 g
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	10
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate, 24%, Lot # 28702. The test substance was composed of 68.0% zirconium 2-ethylhexanoate, 24.2% mineral spirits and 7.8% other ingredients. It was a light yellow liquid with a mineral spirits odor.
Method	:	
Method detail	:	A 0.5 mL portion of material was applied to the intact skin test sites on the guinea pigs. A gauze patch was placed over the treated area and an impervious material was wrapped snugly around the trunks of the animals to hold the patch in place. After 24 hours, the patch was removed, the animals allowed to rest for 1 day, and another application was made to the same skin site. This sequence was repeated for a total of 10 applications, after which time the animals were given a two week rest period. Subsequently a challenge application was put on skin sites differing from the original test sites. The challenge application remained on for 24 hours. The sites were examined for irritation using the Draize method of scoring,

		The sites were examined for irritation using the Draize method of scoring, 24 hours after each induction application and 24 and 48 hours after the challenge application.
Result	:	The test substance was a primary skin irritant and a fatiguing agent, but not a sensitizing agent.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1 (B)) **Metal:** Certain zirconium salts (e.g. zirconium tetrachloride) may cause irritation or caustic injury. Dermal exposure to zirconium in topical poison ivy medications and deodorants has caused subcutaneous granulomas, probably due to a hypersensitivity reaction. (HSDB, 2002).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.2 EYE IRRITATION

Type	:	Primary eye irritation
Guideline/method	:	
Species	:	Rabbits, young adults
Strain	:	Albino
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	Six
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate, 24%, Lot # 28702.
Method	:	
Method detail	:	0.1 mL of the test material was instilled into the right eyes of the animals while the other eye served as the untreated control. The test material was not washed from the eyes. The treated eyes were examined at 1, 2, 3, 5, and 7 days following exposure. Results were scored according to the Draize Scale of Scoring Ocular Lesions.
Result	:	The test substance was not a primary ocular irritant within the definition of the Federal Hazardous Substances Act.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours (See Appendix I: 7.2.2; note study is of low reliability). **Metal:** Zirconium and its compounds are eye irritants (HSDB, 2002).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	

Sex	:
Number of animals	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Post exposure period	:
Doses	:
Control group	:
NOAEL	:
LOAEL	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery.

Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose

group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Appendix I: 7.4(H)). These data are consistent with four previous repeated dose studies in Fischer rats (See Appendix I: 7.4).

In life-time studies in rats in which zirconium sulfate was administered at a level of 5 ppm in their drinking water and in which the solid diet contained an additional 2.6 ppm, state unknown, no evidence was found of any biologic or toxicological activity of zirconium, except to affect the body weight of older animals in an inconsistent manner (HSDB, 2002). It was reported that zirconium oxychloride did not affect the growth of rats and mice after administration of 0.23 g zirconium/kg/day (Delongeas, J.L., Burnel, D., Netter, P., Grignon, M., Mur, J., Royer, R.J. and Grignon, G., 1983. Toxicity and pharmacokinetics of zirconium oxychloride in mice and rats, J. Pharmacol. 14: 437-447).

Metal: In life-time studies in rats in which zirconium sulfate was administered at a level of 5 ppm in their drinking water and in which the solid diet contained an additional 2.6 ppm, state unknown, no evidence was found of any biologic or toxicological activity of zirconium, except to affect the body weight of older animals in an inconsistent manner (HSDB, 2002). It was reported that zirconium oxychloride did not affect the growth of rats and mice after administration of 0.23 g zirconium/kg/day (Delongeas, J.L., Burnel, D., Netter, P., Grignon, M., Mur, J., Royer, R.J. and Grignon, G., 1983. Toxicity and pharmacokinetics of zirconium oxychloride in mice and rats, J. Pharmacol. 14: 437-447).

Reliability :

Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Ames assay, standard plate assay
Species	:	*Salmonella typhimurium*
Strain	:	TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations	:	5, 10, 50, 100, and 500 µg/plate, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254, as per Ames et al., 1975, Mut. Res. 31:347-364. No further details.
Year	:	1981
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Zirconium octoate, Lot No. 28702
Method	:	Followed method of Ames et. al.
Method detail	:	0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37ºC and number of colonies compared to background. No further details provided.
Result	:	Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of *S. typhimurium* tested, either with or without activation. Mutagenic

strains of *S. typhimurium* tested, either with or without activation. Mutagenic index of all five strains was less than 2.0. Positive controls produced the expected response.

Remark : **Supporting data for dissociation products:**
Acid: In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid either with or without activation (See Appendix I: 7.5.1).
Metal: Zirconium oxychloride and zirconium oxychloride hexahydrate have been shown to have no mutagenic activity in the Ames assay, with various strains of *S. typhimurium*, both with and without activation (CCRIS, 2002). No genotoxic effects of zirconium tetrachloride were seen using three *Salmonella* sp. strains or in the SOS chromotest (Couture, P., C. Blaise, D. Cluis and C. Bastien, 1989, Zirconium toxicity assessment using bacteria, algae and fish assays, Water, Air and Soil Pollut. 47: 87-100).

Reliability : [2] Reliable with restrictions. Basic data provided. Comparable to guideline.

Reference : Van Goethem, D., 1981. Evaluation of zirconium octoate in the *Salmonella*/Microsome (Ames) assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

Type : Mutagenicity

Guideline/method :

System of testing : Bacterial DNA damage or repair assay

Species : *Escherichia coli*

Strain : W3110 (pol A^+) and its DNA polymerase deficient derivative p3478 (pol A^-)

Test concentrations : 5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in DMSO.

Cytotoxic concentr. :

Metabolic activation : With and without. Activation with S-9 from Aroclor 1254 induced rat liver as per Ames al., 1975, Mut. Res. 31:347-364

Year : 1981

GLP : No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement

Test substance : Zirconium octoate 24%, Lot No. 28702. Clear liquid, insoluble in water and various solvents. Because of insolubility, the actual material tested was a suspension of zirconium octoate, 24%, in dimethylsulfoxide (DMSO) and the DMSO soluble fraction, if any. Zirconium octoate 24% was suspended with vigorous vortexing in DMSO at 5 mg/mL.

Method : Followed method of Rosenkranz et al. (1971).

Method detail : Test material (5 concentrations) applied to cells in culture. Vehicle controls (DMSO) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 ug/mL without activation and 2-aminofluorene at 200 ug/mL with activation). Bacteria (10^4) of each strain were exposed to the test material for 1 hour at 37ºC. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37ºC and the number of viable cells determined.

Result : Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A^- to pol A^+ survivors), with or without activation. Survival index at all dose levels was greaten than 0.80.

Remark :

Reliability : [2] Reliable with restrictions. Basic data provided. Comparable to guideline.

Reference : Van Goethem, D., 1981. Evaluation of zirconium octoate, 24%, in the *E. coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus mutagenicity assay
Guideline/method	:	
Species	:	Mouse
Strain	:	Specific Pathogen Free mice of the COBS CD-1 (ICR) BR (ICR derived) strain
Sex	:	Male and female
Number of animals	:	5 males and 5 females per dose level (including vehicle control and positive control)
Route of admin.	:	Oral gavage, using corn oil vehicle
Exposure period	:	Thirty hours (dosing at 0 and 24 hours, followed by 6 hours observation)
Doses	:	1250, 2500 and 5000 mg/kg, given twice (24 hours apart) to produce total dose levels of 2500, 5000 and 10000 mg/kg. Corn oil control (0.1 mL/10g via gavage) and positive control (Mitomycin C injected i.p. at 4 mg/kg two times for a total dose of 8 mg/kg).
Year	:	1981
GLP	:	Yes
Test substance	:	Zirconium octoate (24%), [Zirconium 2-ethylhexanoate (24%)], batch #Z8702; specific gravity 1.24; miscible in corn oil.
Method	:	
Method detail	:	Preliminary toxicity study was used to select upper dose for micronucleus test. Animals (18 – 21 g) fasted overnight and orally dosed (two doses, 24 hours apart). Standard volume per dose was 0.1 mL/10 g body weight. At the highest dose, pilo-erection, hypopnea, ptosis, lethargy, and pale external extremities were observed one-half hour after dosing. Two deaths occurred in this group. At the end of 30 hours, all animals were sacrificed. Femurs were cleared and one epiphysis removed from each bone; a bone marrow smear was made onto a slide containing calf serum, cleaned in methanol for 24 hours, air dried, fixed in methanol overnight, air dried, placed in buffer distilled water and stained with Giemsa. The number of micronucleated cells per 1000 polychromatic erythrocytes per animal and the rate of normochromatic to polychromatic erythrocytes was determined. Comparisons to control were made using Wilcoxon's Sum of Ranks test at $p>0.10$.
Result	:	No evidence of mutagenic potential was found. Test material groups produced micronucleated cell counts comparable to the vehicle control and to historical controls (0.1 – 1.8). Positive control response indicated a mean of 60.6 micronucleated cells per 1000 polychromatic erythrocytes. Ratio of normochromatic to polychromatic erythrocytes was comparable in test material and vehicle control groups (1.6). The positive control gave an increased ratio of 4.87.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (See Appendix I: 7.5.3). **Metal:** A single oral administration of an aqueous solution of zirconium oxychloride to mice of both sexes in concentrations 1/20, 1/6 and ½ of the LD50 induced chromosomal abnormalities in bone marrow cells, with the frequencies of aberration directly proportionate to the concentrations used. (HSDB, 2002;Ghosh, S. Sharma, A. and Talukder, G., 1990. Cytotoxic effects of zirconium oxychloride in bone marrow cells of mice. Mutation Research 243(1):29-33). Zirconium oxychloride caused dose-dependent enhancement of the occurrence of chromosomal aberrations and sister chromatid exchanges in human peripheral blood leucocytes (Ghosh, S., and Talukder, G., and Sharma, A. 1991. Cytogenetic effects of exposure to zirconium oxychloride in human leucocyte cultures, 1991. Toxicol. In Vitro 5(4):295-299.)

5(4):295-299.)

Reliability : [2] Reliable with restrictions. Comparable to guideline. Incomplete description of test material.

Reference : Richold, M., Richardson, J.C., and A. Howell, 1981. Micronucleus test on Zirconium Octoate 24% [Zirconium 2-ethylhexanoate (24%)], study conducted for Tenneco Chemicals, Inc. by Huntingdon Research Centre, Huntingdon, England.

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:
Acid: Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (See Appendix I: 7.7.2). In the most reliable study, the NOEL for teratogenic and developmental effects in rats for was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High dose dams experienced hypoactivity, ataxia, and audible

among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight were noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters was significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach

occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(See Appendix I: 7.2.2 (E and F))

Metal: In mice, offspring of dams who received zirconium during pregnancy had long-lasting behavioral changes (HSDB, 2002).

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:
Acid: A One-Generation Reproduction Toxicity Study was conducted with 2-ethylhexanoic acid. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

(See Appendix I: 7.7.1)

Metal: Small fractions of zirconium were absorbed in female rats by the oral route, and the metal seemed to concentrate in the ovaries and produce hypervascularization. (HSDB, 2002)

Reliability :

Reference :

12.1 OTHER INFORMATION

12.2 CARCINOGENICITY

Rats administered 5 ppm of zirconium sulfate in drinking water for the entire lifetime did not have an increased incidence of tumors (HSDB, 2002).

APPENDIX I

ROBUST SUMMARIES and

SIDS DOSSIER for:
2-Ethylhexanoic Acid

••••••••••••••••••••

CAS No. 149-57-5

Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

		Page
SIDS PROFILE		1
SIDS SUMMARY		2
1.0	GENERAL INFORMATION	4
2.0	CHEMICAL IDENTITY	4
	*2.1 CAS NUMBER	4
	*2.2 NAME	4
	2.3 COMMON SYNONYMS	4
	2.4 EMPIRICAL FORMULA	5
	*2.5 STRUCTURAL FORMULA	5
	2.6 PURITY OF INDUSTRIAL PRODUCT	5
	2.6.1 DEGREE OF PURITY	5
	2.6.2 IDENTITY OF MAJOR IMPURITIES	5
	2.6.3 ESSENTIAL ADDITIVES	5
3.0	PHYSICAL-CHEMICAL DATA	5
	*3.1 MELTING OR DECOMPOSITION POINT	5
	*3.2 BOILING POINT	5
	*3.3 VAPOR PRESSURE	6
	*3.4 PARTITION COEFFICIENT N-OCTANOL/WATER	6
	*3.5 WATER SOLUBILITY	7
	3.6 FLASH POINT (LIQUIDS)	7
	3.7 FLAMMABILITY	7
	3.8 PH IN WATER	8
	3.9 OTHER DATA	8
4.0	SOURCE OF EXPOSURE	8
	*4.1 PRODUCTION LEVELS EXPRESSED AS TONNES PER ANNUM	8
	4.2 PROCESSES	8
	*4.3 INFORMATION CONCERNING USES	8
	4.4 OPTIONS FOR DISPOSAL	8
	4.5 OTHER REMARKS	9
5.0	ENVIRONMENTAL FATE AND PATHWAYS	9
	5.1 DEGRADABILITY (BIOTIC AND ABIOTIC)	9
	5.1.1 BIODEGRADABILITY	9
	5.1.2 SEWAGE TREATMENT	10
	5.1.3 STABILITY IN AIR	10
	5.1.4 STABILITY IN WATER	10
	5.1.5 IDENTIFICATIN OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE	10
	5.2 BIOACCUMULATION	11
	5.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS	11
	5.4 MONITORING DATA	11
6.0	ECOTOXICOLOGICAL DATA	11
	6.1 TOXICITY TO FISH	11
	6.1.1 RESULTS OF ACUTE TESTS	11
	6.1.2 RESULTS OF LONG-TERM TESTS	12
	6.2 TOXICITY TO DAPHNIDS	13
	6.2.1 RESULTS OF ACUTE TESTS	13
	6.2.2 RESULTS OF LONG-TERM TESTS	13
	6.3 TOXICITY TO ALGAE	14
	6.4 TOXICITY TO OTHER AQUATIC ORGANISMS	14

Page

6.5 TOXICITY TO BACTERIA 15
*6.6 TOXICITY TO TERRESTRIAL ORGANISMS 15
6.6.1 TOXICITY TO SOIL DWELLING ORGANISMS 15
6.6.2 TOXICITY TO PLANTS 15
6.6.3 TOXICITY TO BIRDS 15
6.7 BIOLOGICAL EFFECTS MONITORING 15
6.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES 15
7.0 TOXICOLOGICAL DATA 15
7.1 ACUTE TOXICITY 15
7.1.1 ACUTE ORAL TOXICITY 16
7.1.2 ACUTE INHALATION TOXICITY 17
7.1.3 ACUTE DERMAL TOXICITY 18
7.2 CORROSIVENESS/IRRITATION 19
7.2.1 SKIN IRRITATION 19
7.2.2 EYE IRRITATION 20
7.3 SKIN SENSITISATION 20
*7.4 REPEATED DOSE TOXICITY 21
*7.5 GENETIC TOXICITY 27
7.5.1 BACTERIAL TEST 27
7.5.2 NON-BACTERIAL IN VITRO TEST 28
7.5.3 NON-BACTERIAL TEST IN VIVO 29
7.6 CARCINOGENICITY 29
*7.7 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY 30
7.7.1 REPRODUCTIVE TOXICITY 30
7.7.2 TERATOGENICITY/DEVELOPMENTAL TOXICITY 32
7.8 SPECIFIC TOXICITIES (NEUROTOXICITY, IMMUNOTOXICITY, ETC.) 41
7.9 TOXICODYNAMICS, TOXICO-KINETICS 41
8.0 EXPERIENCE WITH HUMAN EXPOSURE 43
8.1 BIOLOGICAL MONITORING 43
9.0 RECOMMENDED PRECAUTIONS, CLASSIFICATION, AND SAFETY DATA 44
10.0 AVAILABILITY AND REFERENCE(S) FOR EXISTING REVIEW(S) 44

APPENDIX A 45

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH(CH_2\text{-}CH_3)\text{-}C(=O)\text{-}OH$
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5 STUDY	Info. Available Y/N	OECD Study Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degrability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5 STUDY	Info Available Y/N	OECD Summary Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

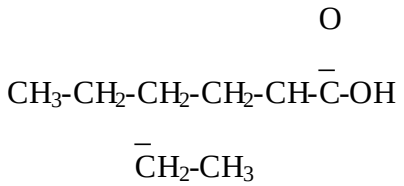
2.3 **Common Synonyms:**

a-Ethylcaproic acid
2-Ethylcaproic acid
a-Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**

$C_8H_{16}O_2$

* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **<u>Physical-Chemical Data</u>**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33×10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]

NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water** (Preferred Study)

log Pow = 3 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup [ ] open cup [X]

Method:

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 **pH in Water**

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES [ ]
NO [X]

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 **Other Data**

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 **Source of Exposure**

* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 **Other Remarks:**

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 **Environmental Fate and Pathways**

* 5.1 **Degradability (Biotic and Abiotic)**

5.1.1 **Biodegradability**

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic [ ]

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, J. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES [ ]
NO [X]

Test Results: BOD_5 = 60 % of Theoretical (2.44 g O_2/g test substance).
BOD_{10} = 76 % of Theoretical (2.44 g O_2/g test substance).
BOD_{20} = 83 % of Theoretical (2.44 g O_2/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 **Sewage Treatment**

Comments: No Data Available.

5.1.3 **Stability in Air** (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES [ ]

NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 **Stability in Water** (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES [ ]
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 **Identification of Main Mode of Degradability in Actual Use**

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES [ ]
NO [X]

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 <u>Ecotoxicological Data</u>

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static [X], semi-static [ ], flow-through [ ]
Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test Results: LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Daphnia magna (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES [ ]
NO [X]

Test Results: 48 hr EC_{50} = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC_0 = 62.5 mg/L, 48 hr EC_{100} = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC_0 - highest tested concentration without effect after 48 hours. EC_{100} - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengessellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES [ ]
NO [X]

Test Results: 72 hr EbC_{10} = 32.543 mg/L
72 hr EbC_{50} = 60.511 mg/L

96 hr EbC_{10} = 24.496 mg/L
96 hr EbC_{50} = 40.616 mg/L

72 hr EuC_{10} = 31.940 mg/L
72 hr EuC_{50} = 49.279 mg/L

96 hr EuC_{10} = 27.938 mg/L
96 hr EuC_{50} = 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

6.5 **Toxicity to Bacteria**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.6 **Toxicity to Terrestrial Organisms**

6.6.1 **Toxicity to Soil Dwelling Organisms**

Test Results: No Data Available.

6.6.2 **Toxicity to Plants**

Test Results: No Data Available.

6.6.3 **Toxicity to Birds**

Test Results: No Data Available.

6.7 **Biological Effects Monitoring (Including Biomagnification)**

Test Results: No Data Available.

6.8 **Biotransformation and Kinetics in Environmental Species**

No Data Available.

7.0 **<u>Toxicological Data</u>** (oral, dermal and inhalation, as appropriate)

* 7.1 **Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES [ ]
NO [X]

Test Results: Discriminating dose (for fixed dose only): LD_{50} = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES [X]
NO [ ]

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 **Acute Dermal Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES [ ]
NO [X]

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance**: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES [X]
NO [ ]

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 Eye Irritation

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES [ ]

NO [X]

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

7.3 Skin Sensitisation

Test Substance:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES [ ]
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES [ ]
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. Toxicol. Lett. 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed

consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized in extremis. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]

NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-

dose groups, respectively. One male from the mid-dose group was found dead during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and

mid-dose groups. Absolute and relative (to body weight) liver weight were significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes),

but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with

the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 Genetic Toxicity

7.5.1 Bacterial test

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: S. typhimurium TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES [ ]

NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES [ ]

NO [ ]

Test Results: No Data Available.

Comments:

Reference:

7.5.3 **Non-Bacterial Test *In Vivo***

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

GLP: YES [X]
NO [ ]

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

Comments: 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. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 **Carcinogenicity**

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]
NO [X]

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were

comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and Postnatal Development in Wistar Rats. Fundam. Appl. Toxicol. in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [ ]
NO [X]

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethyhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratol. 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES [ ]
NO [X]

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryolethality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryolethality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. Life Sci. 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES [ ]
NO [X]

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs

was significantly higher in the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in .the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. Fundam. Appl. Toxicol. 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrlBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour preiod; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

GLP: YES [ ]
NO [X]

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage of resorptions increased at higher dose levels, and was also high in the

animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. Toxicol. Appl. Pharmacol. 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose

group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]

NO [ ]

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption

by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(G.) **Teratogenicity/Developmental toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days (GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into three groups and fed diets as described for the second experiment. The

animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg)was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. Teratology 53(2):p88, Abstract 21.

7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

7.9 Toxicodynamics, Toxico-Kinetics

Test Substance: [2-^{14}C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmole) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO [ ]

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid

		7% unmetabolized 2-Ethylhexanoic acid
Oral	***100 mg/kg***	***12% glucuronide-2-Ethylhexanoic acid***
	(Repeated)	12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 **Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m^3 (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of

approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid elimination of the material. No urine samples were collected during the work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be 2-2.33 x 10^{-4} mg/kilogram body weight/8 hour workday. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. Int. Arch. Occup. Environ. Health, 62:213-216.

9.0 Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 Availability and Reference(s) for Existing Review(s)

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

1. General Information

ID 22464-99-9

Date December 20, 2002

Note: Appendix I is Robust Summaries and SIDS Dossier for 2-ethylhexanoic acid.

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, zirconium salt
Chemical Name	:	Hexanoic acid, 2-ethyl, zirconium salt
CAS Registry No.	:	22464-99-9
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$C_{16}H_{30}O_5Zr$
Molecular Weight	:	393.63
Synonyms and Tradenames	:	Zirconium 2-ethylhexanoate; Zirconium octoate; Zirconyl 2-ethylhexanoate; Zirconium versalate liquid, 24%
References	:	http://www.chemfinder.com; MSDS prepared by The Shepherd Chemical Company, dated 5/15/01.

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Melting point is reported as –118.4°C for 2-ethylhexanoic acid (See Appendix I: 3.1)
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	> 300 °F (relative to mineral spirits)
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (See Appendix I.: 3.2)
Reliability	:	
Reference	:	MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	1.28
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference		MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	2.0 mm Hg (relative to mineral spirits)
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Vapor pressure is reported as 1.33 x 10^{-3} kPa at 20°C for 2-ethylhexanoic acid (See Appendix I: 3.3)
Reliability	:	
Reference	:	MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (See Appendix I: 3.4).
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	Negligible
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Deg. products CAS#	:	
Method	:	

Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The water solubility of 2-ethylhexanoic acid was reported to be 25 mg/L at 25°C (See Appendix I: 3.5).
Reliability	:	
Reference	:	MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	106 °F (PMcc)
Year	:	
GLP	:	
Test substance	:	Zirconium versalate liquid, 24% (24% metal); Mixture of zirconium 2-ethylhexanoate (75-85% by weight) and mineral spirits (Stoddard)
Method	:	Closed cup
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** A flashpoint of 118°C was reported for 2-ethylhexanoic acid (See Appendix I: 3.6).
Reliability	:	
Reference	:	MSDS dated 5/15/01, prepared by The Shepherd Chemical Company

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	5.81, 7.09. 7.65, and 8.24 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Zirconium (IV) 2-ethylhexanoate, lot number 119L09, received from Alfa Aesar Chemical Company. Liquid, purity of 18.17% ZrO2.
Approximate water solubility	:	50 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of zirconium(IV) 2-ethylhexanoate were prepared at a nominal concentration of 25 mg/L by fortification of degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in tetrahydrofuran. Each sample was titrated against 0.001N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the first equivalence point and thereafter, a minimum of three incremental additions were made before each of the three remaining equivalence points. The titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 3 points for each equivalence point on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.

Result	:	Mean (N = 3) pKa values were 5.81 (SD = 0.0806), 7.09 (SD = 0.0491), 7.65 (SD = 0.0689), and 8.24 (SD = 0.0299) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of zirconium (IV) 2-ethylhexanoate, Wildlife International, Ltd. Study No. 534C-104, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	mg/l
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % %

		%
Control substance	:	
Kinetic	:	%
		%
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Aerobic biodegradation of 2-ethylhexanoic acid was reported with BOD_5, BOD_{10} and BOD_{20} at 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (See Appendix I: 5.1.1).
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type	:	Acute toxicity to fish. Static exposure.
Guideline/method	:	
Species	:	*Lepomis macrochirus* (bluegill sunfish, freshwater)
Exposure period	:	96 hours
NOEC	:	
LC0	:	
LC50	:	LC50 greater than tested concentration (100% of a 24% zirconium octoate solution).
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	:	Test concentrations were control and 100% concentration of a 24% zirconium octoate solution. Test conducted in reconstituted freshwater (hardness = soft water) and temperature range of 19 – 22.5ºC. Fish were < 1 year old and of same age class. Biological loading was 0.3 g/L.
Result	:	No mortality observed in 100% concentration of a 24% calcium octoate solution.
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h LC50 for fathead minnows (*Pimephales promelas*) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix I: 6.1.1). **Metal:** For zirconium tetrachloride, the 96-h LC50 for rainbow trout (*Oncorhynchus mykiss*) was reported to be greater than 20 mg Zr/L; for the zirconium salt of sulfuric acid, the 96-h LC50 for *Pimephales promelas* was reported to be 14 – 145 mg Zr/L; for zirconium oxychloride, the 96-h LC50 for *Lepomis macrochirus* was reported to be 15 – 270 mg Zr/L and for *Pimephales promelas*, 18 –240 mg Zr/L. (ECOTOX database, 2002).
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished, and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

Type	:	Acute toxicity to fish. Static exposure.
Guideline/method	:	
Species	:	*Cyprinodon variegatus* (sheepshead minnow, saltwater)
Exposure period	:	96 hours
NOEC	:	
LC0	:	

LC50	:	LC50 greater than tested concentration (100% of a 24% zirconium octoate solution).
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Fish, 365-0
Method detail	:	Test concentrations were control and 100% concentration of a 24% zirconium octoate solution. Test conducted using synthetic seawater (28 ppt), temperature range of 20 - 22ºC, fish < 1 yr old and of same age class, biological loading 0.9 g/L.
Result	:	No mortality observed in 100% concentration of a 24% calcium octoate solution.
Remark	:	
Reliability	:	[3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished, and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.
Reference	:	Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Acute toxicity to daphnids. Static exposure.
Guideline/method	:	
Species	:	*Daphnia magna*
Exposure period	:	48 hours
NOEC	:	
EC0	:	
EC50	:	48-h EC50: 58.1% (95% CI: 46 - 73.3%)
EC100	:	
Other	:	24-h EC50 could not be estimated because of insufficient mortality
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	Not reported
Test substance	:	Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method	:	United States Testing Company protocol PRO/FT, Daphnia, 365-0
Method detail	:	Test conducted in filtered (0.22 µ) lake water (hardness = soft), temperature range 19 - 21ºC. Test concentrations were 0, 10, 18, 32, 56 and 100% of zirconium octoate (24% solution). No information on test organisms.

zirconium octoate (24% solution). No information on test organisms.

Result : 48-h EC50: 58.1% (95% CI: 46 – 73.3%); 24-h EC50: could not be calculated because of low mortality

Remark : **Supporting data for dissociation products:**
Acid: The 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (See Appendix I: 6.2.1).
Metal: For zirconium chloride, the 3-week LC50 for *Daphnia magna* was reported to be 2 mg Zr/L (ECOTOX database, 2002).

Reliability : [3] Not reliable. Test material inadequately described and reported to be not soluble in water, with no details given as to how exposure of test organisms was accomplished and no analytical verification of test concentrations. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Lack of detail on methods. Secondary reference.

Reference : Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type : Algal acute toxicity test
Guideline/method :
Species : *Selenastrum capricornutum* (freshwater green alga)
Endpoint : „growth“ (not specified further; could be growth rate, yield or viability)
Exposure period : 96 hours
NOEC :
LOEC :
EC0 :
EC10 :
EC50 : 0.07%
Other :
Other :
Other :
Limit test :
Analytical monitoring : None reported
Year : 1981
GLP : Not reported
Test substance : Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.
Method : United States Testing Company protocol PRO/FT, Algae, 357-0
Method detail : Test concentrations were 0, 0.6, 0.10, 0.18, 0.32 and 0.56%. Stock solution prepared by adding an excessive amount of zirconium octoate (24%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used freshwater algal maintenance medium and test temperature 19 - 20ºC.
Result : 96-h EC50 was 0.07%
Remark : **Supporting data for dissociation products:**
Acid: The 96-h E_bC50 (EC50 based upon biomass) for the green alga *Scenedesmus subspicatus* was reported to be 40.616 mg/L for 2-ethylhexanoic acid (See Appendix I: 6.3).
Metal: For zirconium tetrachloride, the 96-h EC50 for *Selenastrum capricornutum* was reported to be 2.6 mg Zr/L (ECOTOX database, 2002).

capricornutum was reported to be 2.6 mg Zr/L (ECOTOX database, 2002).

Reliability : [3] Not reliable. Test material inadequately described and reported to be not soluble in water. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Non-standard test conditions, lack of detail on methods. Secondary reference.

Reference : Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

Type : Algal acute toxicity test

Guideline/method :

Species : *Skeletonema costatum* (saltwater diatom)

Endpoint : „growth“ (not specified further; could be growth rate, yield or viability)

Exposure period : 96 hours

NOEC :

LOEC :

EC0 :

EC10 :

EC50 : 0.08%

Other :

Other :

Other :

Limit test :

Analytical monitoring : None reported

Year : 1981

GLP : Not reported

Test substance : Zirconium octoate (24%), Lot No. E181-168B, supplied by sponsor (Tenneco Chemicals, Park 80 Plaza West –1, Saddle Brook, NJ). Clear yellow liquid, reported as not soluble in water. Purity not reported.

Method : United States Testing Company protocol PRO/FT, Algae, 357-0

Method detail : Test concentrations were 0, 0.6, 0.10, 0.18, 0.32 and 0.56%. Stock solution prepared by adding an excessive amount of zirconium octoate (24%) to the algal assay medium, stirring for five minutes, and filtering through several layers of cotton gauze into a clean container. This solution was considered to be a saturated solution from which test dilutions were made. Used seawater algal medium I and test temperature 19 - 20ºC

Result : 96-h EC50 was 0.08%

Remark :

Reliability : [3] Not reliable. Test material inadequately described and reported to be not soluble in water. Test concentrations reported as percent dilution not mass per volume concentration, confounding interpretation. Non-standard procedures used to prepare test solutions, with no analytical confirmation of test concentrations. Non-standard test conditions, lack of detail on methods. Secondary reference.

Reference : Previously abstracted information from studies conducted for Tenneco Chemicals, Park 80 Plaza West - 1, Saddle Brook, NJ by United States Testing Company, Hoboken, NJ. (Study No. 03498). Original study report not available.

4.4 ACUTE TOXICITY TO AVIAN SPECIES

Type : Limit test

Guideline/method	:	
Species	:	Bobwhite quail (*Colinus virginianus*)
Number, sex and age of animals	:	22 birds (11 males and 11 females), approximately 16 weeks old (200 ± 30 g)
Exposure period	:	14 days
NOEL	:	
LD50	:	> 2000 mg/kg
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	None reported
Year	:	1981
GLP	:	No
Test substance	:	Zirconium octoate, administered as a 20% w/v suspension in corn oil
Method	:	
Method detail	:	Birds were housed in metal cages with wire floors, under a photoperiod of 17 hours light and 7 hours dark, mean humidity of 71% and mean temperature of 20°C (range 14 - 28°C). Birds were provided with water and standard diet ad libitum (except overnight starvation prior to dosing). Dose levels included vehicle control and 2000 mg/kg, administered by oral gavage. Mortalities were recorded daily. Body weights were recorded prior to dosing and at days 3, 7 and 14. Food consumption was recorded weekly. All birds were examined at death or test termination for gross pathology.
Result	:	Following dosing, birds dosed with zirconium octoate were quiet and subdued, but recovered after 19 hours and remained in good health for the rest of the study. Body weight changes were considered to be within normal limits. Food consumption was similar in the dosed birds and the controls. No abnormalities were detected in any birds.
Remark	:	
Reliability	:	[3] Not reliable. Test material inadequately described. Secondary reference.
Reference	:	Previously abstracted information from studies conducted by Huntingdon Research Centre, Huntingdon, Cambridgeshire, England. Original study report not available.

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:
Type	:
Guideline/method	:
Species	:
Number of animals	:
Males	:
Females	:
Doses	:
Males	:
Females	:
Vehicle	:
Route of administration	:
Exposure time	:
Product type guidance	:
Decision on results on acute tox. tests	:
Adverse effects on prolonged exposure	:
Half-lives	: 1st: 2nd: 3rd:
Toxic behavior	:
Deg. product	:
Deg. products CAS#	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and

1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid
		7% glucuronide-diacid or hydroxylated 2- Ethylhexanoic acid
		2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid
		14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid
		12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid
		3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid

		3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid
		9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Metal: Zirconium salts when parenterally administered are slowly absorbed from injection sites and simple cationic salts cause local irritation. Intravenously injected cationic salts form insoluble colloidal polymers and are phagocytized by macrophages. Young rats absorb more parenterally injected zirconium salts than adult or old animals, and young rats retain them longer in their skeleton because of vigorous metabolism in bone marrow. Excretion is mainly through feces, owing to poor alimentary absorption of orally-ingested zirconium salts and to the accumulation of soluble zirconium salts in the liver with their subsequent return to the alimentary tract by the bile. Less than 1% of the daily intake of zirconium of humans is excreted in urine. Absorbed zirconium is either sequestered in the skeleton or excreted very rapidly. A mechanism of zirconium homeostasis is apparently present in humans. (Hazardous Substances Data Bank, online at , subsequently referred to as HSDB, 2002). The biochemical properties of zirconium include a high affinity for phosphate groups and an inhibitory effect on many enzymes (Couture, P., C. Blaise, D. Cluis and C. Bastien, 1989, Zirconium toxicity assessment using bacteria, algae and fish assays, Water, Air and Soil Pollut. 47: 87-100)..

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type : Limit Test
Guideline/Method :
Species : Rat
Strain : Sherman-Wistar albino
Sex : Male and female
Number of animals : 10 (5 male, 5 female)
Vehicle :
Doses : 5.0 g/kg
LD50 : >5.0 g/kg for both males and females.
Year : 1980
GLP : Not reported
Test substance : Zirconium octoate, 24%, Lot # 28702. Density approx. 1.3 g/mL.
Method : Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.3.
Method detail : Animals (200 - 300 g) fasted overnight (food only) prior to dosing, weighed and administered the test material (as received) via intragastric intubation. Observed for 14-days post-exposure.
Result : No mortality observed. LD50 for both sexes > 5.0 g/kg For both sexes, within 1 hr following dosing, animals were slightly ataxic, depressed, ruffled, and drooling. After 2-3 hours they were semi-comatose to comatose. They remained severely depressed, ruffled, drooling and dirty for 2-3 days before

		beginning to recover. After 5 days the animals appeared essentially normal. Gross necropsies were unremarkable.
Remark	:	**Supporting data for dissociation products:** **Acid:** The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (See Appendix I: 7.1.1). **Metal:** Zirconium salts have low oral toxicity; both the tetrachloride and oxychloride are poorly adsorbed and therefore have low oral toxicities with LD50 values in the rat of 0.7 g/kg and 3.5 g/kg, respectively. Toxicity is increased by intraperitoneal injection (LC50 of 400 mg/kg in rats for zirconium oxychloride). (HSDB, 2002)
Reliability	:	[2] Reliable with restrictions. Basic data provided, exposure conditions not fully described, test material not described. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), study conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	Limit Test
Guideline/method	:	
Species	:	Rat
Strain	:	Albino
Sex	:	Male and female
Number of animals	:	10 (5 male and 5 female)
Vehicle	:	
Doses	:	One concentration, 8.8 mg/L of a 50% w/v suspension in mineral spirits. Median particle diameter measured to ensure a respirable dose was received.
Exposure time	:	1 hour
LC50	:	> 8.8 mg/L (maximum attainable nominal concentration)
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate 24% (Lot # 28702), prepared and used as a 50% w/v suspension in mineral spirits.
Method	:	
Method detail	:	Animals (200 – 210 g, average) were exposed to the test material inside a 260-L Plexiglas exposure chamber for 1 hour. Presumably whole body exposure, though not described in report. An aerosol was generated by a jet collision nebulizer; air was passed through the test material and into the chamber at 20 L/min., at 70ºF. Test material concentration was measured and determined to be 8.8 mg/L (determined by weighing the flask containing the aerosol before and after exposure). Particle size, determined for 5 minutes midway through the exposure period, was calculated to be 0.68 microns MMD (mass median diameter). Animals observed for 14 days post-exposure
Result	:	No adverse effects were observed during the exposure period or during the two-week post exposure period. No mortality, no toxicity, and no adverse gross necropsy findings
Remark	:	**Supporting data for dissociation products:** **Acid:** The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (See Appendix I: 7.1.2). **Metal:** Severe, persistent interstitial pneumonitis has been produced in experimental animals exposed to airborne zirconium concentrations of 5 mg/m3 (HSDB, 2002).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Exposure conditions not described, duration of exposure and determination of measured test concentrations less than current guidelines require.

concentrations less than current guidelines require.

Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.1.3 ACUTE DERMAL TOXICITY

Type : Limit Test
Guideline/method :
Species : Rabbit
Strain : Albino
Sex : Male and female
Number of animals : Six (3 male and 3 female)
Vehicle :
Doses : One dose, 5 g/kg
LD50 : > 5 g/kg
Year : 1980
GLP : Not reported
Test substance : Zirconium octoate, 24%, Lot # 28702. Density approx. 1.3 g/mL.
Method : Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.40.
Method detail : Animals (2-3 kg) had their backs clipped free of hair and abraded 24 hours prior to dose administration. Each animal was weighed and the appropriate amount of test material applied to the back, covered with gauze and impervious damming. Dressings were removed after 24 hours, excess material removed, and backs wiped clean. Animals observed for 14 days post-exposure. Gross autopsies conducted on all dead and surviving animals.
Result : No mortality or toxicity. No adverse gross necropsy findings in this limit test.
Remark : **Supporting data for dissociation products:**
Acid: The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted) was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg.(See Appendix I: 7.1.3)
Metal: No data
Reliability : [2] Reliable with restrictions. Basic data provided. Exposure conditions not fully described, size of area of application not mentioned. Comparable to guideline.
Reference : Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.2 SKIN IRRITATION

Type : Primary skin irritation
Guideline/method :
Species : Rabbit, albino
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals : Six
Vehicle :
Classification : Not classified as a primary skin irritant

Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate, 24%, Lot # 28702
Method	:	Tested in accordance with Federal Hazardous Substances Act, 16 CFR Section 1500.41.
Method detail	:	Rabbits were clipped over a wide area. One side of the animals' backs was abraded at one site with a lancet sufficiently deep to penetrate the stratum corneum but not enter the derma to produce bleeding. A 0.5 mL portion of the test material was applied to an abraded and an intact skin site on the same animal. The treated areas were covered with gauze patches and an impervious material was wrapped around the trunks to hold the patches in place. After 24 hours, the wrapping was removed and the treated areas examined. Readings were also made after 72 hours. The Draize method of scoring was used.
Result	:	The test substance was not a primary skin irritant to rabbits within the definition of the Federal Hazardous Substances Act. The primary irritation score was 0.96.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1 (B)) **Metal:** Certain zirconium salts (e.g. zirconium tetrachloride) may cause irritation or caustic injury. Dermal exposure to zirconium in topical poison ivy medications and deodorants has caused subcutaneous granulomas, probably due to a hypersensitivity reaction. (HSDB, 2002).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

Type	:	Contact dermal irritation/sensitization
Guideline/method	:	
Species	:	Guinea pig
Strain	:	
Sex	:	Male, weighing 300 – 400 g
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	10
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate, 24%, Lot # 28702. The test substance was composed of 68.0% zirconium 2-ethylhexanoate, 24.2% mineral spirits and 7.8% other ingredients. It was a light yellow liquid with a mineral spirits odor.
Method	:	
Method detail	:	A 0.5 mL portion of material was applied to the intact skin test sites on the guinea pigs. A gauze patch was placed over the treated area and an impervious material was wrapped snugly around the trunks of the animals to hold the patch in place. After 24 hours, the patch was removed, the animals allowed to rest for 1 day, and another application was made to the same skin site. This sequence was repeated for a total of 10 applications, after which time the animals were given a two week rest period. Subsequently a challenge application was put on skin sites differing from the original test sites. The challenge application remained on for 24 hours. The sites were examined for irritation using the Draize method of scoring,

		The sites were examined for irritation using the Draize method of scoring, 24 hours after each induction application and 24 and 48 hours after the challenge application.
Result	:	The test substance was a primary skin irritant and a fatiguing agent, but not a sensitizing agent.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1 (B)) **Metal:** Certain zirconium salts (e.g. zirconium tetrachloride) may cause irritation or caustic injury. Dermal exposure to zirconium in topical poison ivy medications and deodorants has caused subcutaneous granulomas, probably due to a hypersensitivity reaction. (HSDB, 2002).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.2.2 EYE IRRITATION

Type	:	Primary eye irritation
Guideline/method	:	
Species	:	Rabbits, young adults
Strain	:	Albino
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	Six
Vehicle	:	
Classification	:	
Year	:	1980
GLP	:	Not reported
Test substance	:	Zirconium octoate, 24%, Lot # 28702.
Method	:	
Method detail	:	0.1 mL of the test material was instilled into the right eyes of the animals while the other eye served as the untreated control. The test material was not washed from the eyes. The treated eyes were examined at 1, 2, 3, 5, and 7 days following exposure. Results were scored according to the Draize Scale of Scoring Ocular Lesions.
Result	:	The test substance was not a primary ocular irritant within the definition of the Federal Hazardous Substances Act.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours (See Appendix I: 7.2.2; note study is of low reliability). **Metal:** Zirconium and its compounds are eye irritants (HSDB, 2002).
Reliability	:	[2] Reliable with restrictions. Basic data provided. Comparable to guideline.
Reference	:	Biosearch, Inc., Philadelphia, PA. (Study no. 80-1975A), conducted for Tenneco Chemicals, Inc., Saddle Brook, NJ.

5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	

Sex	:
Number of animals	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Post exposure period	:
Doses	:
Control group	:
NOAEL	:
LOAEL	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery.

Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose

group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Appendix I: 7.4(H)). These data are consistent with four previous repeated dose studies in Fischer rats (See Appendix I: 7.4).

In life-time studies in rats in which zirconium sulfate was administered at a level of 5 ppm in their drinking water and in which the solid diet contained an additional 2.6 ppm, state unknown, no evidence was found of any biologic or toxicological activity of zirconium, except to affect the body weight of older animals in an inconsistent manner (HSDB, 2002). It was reported that zirconium oxychloride did not affect the growth of rats and mice after administration of 0.23 g zirconium/kg/day (Delongeas, J.L., Burnel, D., Netter, P., Grignon, M., Mur, J., Royer, R.J. and Grignon, G., 1983. Toxicity and pharmacokinetics of zirconium oxychloride in mice and rats, J. Pharmacol. 14: 437-447).

Metal: In life-time studies in rats in which zirconium sulfate was administered at a level of 5 ppm in their drinking water and in which the solid diet contained an additional 2.6 ppm, state unknown, no evidence was found of any biologic or toxicological activity of zirconium, except to affect the body weight of older animals in an inconsistent manner (HSDB, 2002). It was reported that zirconium oxychloride did not affect the growth of rats and mice after administration of 0.23 g zirconium/kg/day (Delongeas, J.L., Burnel, D., Netter, P., Grignon, M., Mur, J., Royer, R.J. and Grignon, G., 1983. Toxicity and pharmacokinetics of zirconium oxychloride in mice and rats, J. Pharmacol. 14: 437-447).

Reliability :

Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	
System of testing	:	Ames assay, standard plate assay
Species	:	*Salmonella typhimurium*
Strain	:	TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations	:	5, 10, 50, 100, and 500 µg/plate, in duplicate. Dissolved in ethanol.
Cytotoxic concentr.	:	
Metabolic activation	:	Conducted both with and without activation. S-9 fraction derived from rats induced with Aroclor 1254, as per Ames et al., 1975, Mut. Res. 31:347-364. No further details.
Year	:	1981
GLP	:	No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement
Test substance	:	Zirconium octoate, Lot No. 28702
Method	:	Followed method of Ames et. al.
Method detail	:	0.1 mL aliquots of test material at 5 concentrations were used. Positive controls and vehicle controls (ethanol) included. Plates incubated for 48 hours at 37ºC and number of colonies compared to background. No further details provided.
Result	:	Negative. Test material did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for all strains of *S. typhimurium* tested, either with or without activation. Mutagenic

strains of *S. typhimurium* tested, either with or without activation. Mutagenic index of all five strains was less than 2.0. Positive controls produced the expected response.

Remark : **Supporting data for dissociation products:**
Acid: In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid either with or without activation (See Appendix I: 7.5.1).
Metal: Zirconium oxychloride and zirconium oxychloride hexahydrate have been shown to have no mutagenic activity in the Ames assay, with various strains of *S. typhimurium*, both with and without activation (CCRIS, 2002). No genotoxic effects of zirconium tetrachloride were seen using three *Salmonella* sp. strains or in the SOS chromotest (Couture, P., C. Blaise, D. Cluis and C. Bastien, 1989, Zirconium toxicity assessment using bacteria, algae and fish assays, Water, Air and Soil Pollut. 47: 87-100).

Reliability : [2] Reliable with restrictions. Basic data provided. Comparable to guideline.

Reference : Van Goethem, D., 1981. Evaluation of zirconium octoate in the *Salmonella*/Microsome (Ames) assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

Type : Mutagenicity

Guideline/method :

System of testing : Bacterial DNA damage or repair assay

Species : *Escherichia coli*

Strain : W3110 (pol A^+) and its DNA polymerase deficient derivative p3478 (pol A^-)

Test concentrations : 5, 10, 50, 100, and 500 µg/mL, in duplicate. Dissolved in DMSO.

Cytotoxic concentr. :

Metabolic activation : With and without. Activation with S-9 from Aroclor 1254 induced rat liver as per Ames al., 1975, Mut. Res. 31:347-364

Year : 1981

GLP : No. GLP is mentioned in attached protocol, but report does not include GLP compliance statement

Test substance : Zirconium octoate 24%, Lot No. 28702. Clear liquid, insoluble in water and various solvents. Because of insolubility, the actual material tested was a suspension of zirconium octoate, 24%, in dimethylsulfoxide (DMSO) and the DMSO soluble fraction, if any. Zirconium octoate 24% was suspended with vigorous vortexing in DMSO at 5 mg/mL.

Method : Followed method of Rosenkranz et al. (1971).

Method detail : Test material (5 concentrations) applied to cells in culture. Vehicle controls (DMSO) included. Positive controls included (N-methyl-N'-nitrosoguanidine at 2 ug/mL without activation and 2-aminofluorene at 200 ug/mL with activation). Bacteria (10^4) of each strain were exposed to the test material for 1 hour at 37ºC. Then 0.1 mL aliquots were removed and plated on agar, with and without activation, incubated for 18 hours at 37ºC and the number of viable cells determined.

Result : Negative. No dose-response was observed and there was no decrease in survival index (ratio of pol A^- to pol A^+ survivors), with or without activation. Survival index at all dose levels was greaten than 0.80.

Remark :

Reliability : [2] Reliable with restrictions. Basic data provided. Comparable to guideline.

Reference : Van Goethem, D., 1981. Evaluation of zirconium octoate, 24%, in the *E. coli* DNA Repair-Suspension Assay. Study conducted for Tenneco Chemicals, Inc. by Midwest Research Institute, Kansas City, MO (Study No. 4822-E).

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus mutagenicity assay
Guideline/method	:	
Species	:	Mouse
Strain	:	Specific Pathogen Free mice of the COBS CD-1 (ICR) BR (ICR derived) strain
Sex	:	Male and female
Number of animals	:	5 males and 5 females per dose level (including vehicle control and positive control)
Route of admin.	:	Oral gavage, using corn oil vehicle
Exposure period	:	Thirty hours (dosing at 0 and 24 hours, followed by 6 hours observation)
Doses	:	1250, 2500 and 5000 mg/kg, given twice (24 hours apart) to produce total dose levels of 2500, 5000 and 10000 mg/kg. Corn oil control (0.1 mL/10g via gavage) and positive control (Mitomycin C injected i.p. at 4 mg/kg two times for a total dose of 8 mg/kg).
Year	:	1981
GLP	:	Yes
Test substance	:	Zirconium octoate (24%), [Zirconium 2-ethylhexanoate (24%)], batch #Z8702; specific gravity 1.24; miscible in corn oil.
Method	:	
Method detail	:	Preliminary toxicity study was used to select upper dose for micronucleus test. Animals (18 – 21 g) fasted overnight and orally dosed (two doses, 24 hours apart). Standard volume per dose was 0.1 mL/10 g body weight. At the highest dose, pilo-erection, hypopnea, ptosis, lethargy, and pale external extremities were observed one-half hour after dosing. Two deaths occurred in this group. At the end of 30 hours, all animals were sacrificed. Femurs were cleared and one epiphysis removed from each bone; a bone marrow smear was made onto a slide containing calf serum, cleaned in methanol for 24 hours, air dried, fixed in methanol overnight, air dried, placed in buffer distilled water and stained with Giemsa. The number of micronucleated cells per 1000 polychromatic erythrocytes per animal and the rate of normochromatic to polychromatic erythrocytes was determined. Comparisons to control were made using Wilcoxon's Sum of Ranks test at p>0.10.
Result	:	No evidence of mutagenic potential was found. Test material groups produced micronucleated cell counts comparable to the vehicle control and to historical controls (0.1 – 1.8). Positive control response indicated a mean of 60.6 micronucleated cells per 1000 polychromatic erythrocytes. Ratio of normochromatic to polychromatic erythrocytes was comparable in test material and vehicle control groups (1.6). The positive control gave an increased ratio of 4.87.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (See Appendix I: 7.5.3). **Metal:** A single oral administration of an aqueous solution of zirconium oxychloride to mice of both sexes in concentrations 1/20, 1/6 and ½ of the LD50 induced chromosomal abnormalities in bone marrow cells, with the frequencies of aberration directly proportionate to the concentrations used. (HSDB, 2002;Ghosh, S. Sharma, A. and Talukder, G., 1990. Cytotoxic effects of zirconium oxychloride in bone marrow cells of mice. Mutation Research 243(1):29-33). Zirconium oxychloride caused dose-dependent enhancement of the occurrence of chromosomal aberrations and sister chromatid exchanges in human peripheral blood leucocytes (Ghosh, S., and Talukder, G., and Sharma, A. 1991. Cytogenetic effects of exposure to zirconium oxychloride in human leucocyte cultures, 1991. Toxicol. In Vitro 5(4):295-299.)

5(4):295-299.)

Reliability : [2] Reliable with restrictions. Comparable to guideline. Incomplete description of test material.

Reference : Richold, M., Richardson, J.C., and A. Howell, 1981. Micronucleus test on Zirconium Octoate 24% [Zirconium 2-ethylhexanoate (24%)], study conducted for Tenneco Chemicals, Inc. by Huntingdon Research Centre, Huntingdon, England.

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:
Acid: Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (See Appendix I: 7.7.2). In the most reliable study, the NOEL for teratogenic and developmental effects in rats for was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible

among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight were noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters was significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsals, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach

occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(See Appendix I: 7.2.2 (E and F))

Metal: In mice, offspring of dams who received zirconium during pregnancy had long-lasting behavioral changes (HSDB, 2002).

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :

Supporting data for dissociation products:
Acid: A One-Generation Reproduction Toxicity Study was conducted with 2-ethylhexanoic acid. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

(See Appendix I: 7.7.1)

Metal: Small fractions of zirconium were absorbed in female rats by the oral route, and the metal seemed to concentrate in the ovaries and produce hypervascularization. (HSDB, 2002)

Reliability :

Reference :

12.3 OTHER INFORMATION

12.4 CARCINOGENICITY

Rats administered 5 ppm of zirconium sulfate in drinking water for the entire lifetime did not have an increased incidence of tumors (HSDB, 2002).

APPENDIX I

ROBUST SUMMARIES and

SIDS DOSSIER for:
2-Ethylhexanoic Acid

••••••••••••••••••••

CAS No. 149-57-5

Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

		Page
SIDS PROFILE		1
SIDS SUMMARY		2
1.0	GENERAL INFORMATION	4
2.0	CHEMICAL IDENTITY	4
	*2.1 CAS NUMBER	4
	*2.2 NAME	4
	2.3 COMMON SYNONYMS	4
	2.4 EMPIRICAL FORMULA	5
	*2.5 STRUCTURAL FORMULA	5
	2.6 PURITY OF INDUSTRIAL PRODUCT	5
	2.6.1 DEGREE OF PURITY	5
	2.6.2 IDENTITY OF MAJOR IMPURITIES	5
	2.6.3 ESSENTIAL ADDITIVES	5
3.0	PHYSICAL-CHEMICAL DATA	5
	*3.1 MELTING OR DECOMPOSITION POINT	5
	*3.2 BOILING POINT	5
	*3.3 VAPOR PRESSURE	6
	*3.4 PARTITION COEFFICIENT N-OCTANOL/WATER	6
	*3.5 WATER SOLUBILITY	7
	3.6 FLASH POINT (LIQUIDS)	7
	3.7 FLAMMABILITY	7
	3.8 PH IN WATER	8
	3.9 OTHER DATA	8
4.0	SOURCE OF EXPOSURE	8
	*4.1 PRODUCTION LEVELS EXPRESSED AS TONNES PER ANNUM	8
	4.2 PROCESSES	8
	*4.3 INFORMATION CONCERNING USES	8
	4.4 OPTIONS FOR DISPOSAL	8
	4.5 OTHER REMARKS	9
5.0	ENVIRONMENTAL FATE AND PATHWAYS	9
	5.1 DEGRADABILITY (BIOTIC AND ABIOTIC)	9
	5.1.1 BIODEGRADABILITY	9
	5.1.2 SEWAGE TREATMENT	10
	5.1.3 STABILITY IN AIR	10
	5.1.4 STABILITY IN WATER	10
	5.1.5 IDENTIFICATIN OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE	10
	5.2 BIOACCUMULATION	11
	5.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS	11
	5.4 MONITORING DATA	11
6.0	ECOTOXICOLOGICAL DATA	11
	6.1 TOXICITY TO FISH	11
	6.1.1 RESULTS OF ACUTE TESTS	11
	6.1.2 RESULTS OF LONG-TERM TESTS	12
	6.2 TOXICITY TO DAPHNIDS	13
	6.2.1 RESULTS OF ACUTE TESTS	13
	6.2.2 RESULTS OF LONG-TERM TESTS	13
	6.3 TOXICITY TO ALGAE	14
	6.4 TOXICITY TO OTHER AQUATIC ORGANISMS	14

Page

6.5 TOXICITY TO BACTERIA 15
*6.6 TOXICITY TO TERRESTRIAL ORGANISMS 15
6.6.1 TOXICITY TO SOIL DWELLING ORGANISMS 15
6.6.2 TOXICITY TO PLANTS 15
6.6.3 TOXICITY TO BIRDS 15
6.7 BIOLOGICAL EFFECTS MONITORING 15
6.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES 15
7.0 TOXICOLOGICAL DATA 15
7.1 ACUTE TOXICITY 15
7.1.1 ACUTE ORAL TOXICITY 16
7.1.2 ACUTE INHALATION TOXICITY 17
7.1.3 ACUTE DERMAL TOXICITY 18
7.2 CORROSIVENESS/IRRITATION 19
7.2.1 SKIN IRRITATION 19
7.2.2 EYE IRRITATION 20
7.3 SKIN SENSITISATION 20
*7.4 REPEATED DOSE TOXICITY 21
*7.5 GENETIC TOXICITY 27
7.5.1 BACTERIAL TEST 27
7.5.2 NON-BACTERIAL IN VITRO TEST 28
7.5.3 NON-BACTERIAL TEST IN VIVO 29
7.6 CARCINOGENICITY 29
*7.7 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY 30
7.7.1 REPRODUCTIVE TOXICITY 30
7.7.2 TERATOGENICITY/DEVELOPMENTAL TOXICITY 32
7.8 SPECIFIC TOXICITIES (NEUROTOXICITY, IMMUNOTOXICITY, ETC.) 41
7.9 TOXICODYNAMICS, TOXICO-KINETICS 41
8.0 EXPERIENCE WITH HUMAN EXPOSURE 43
8.1 BIOLOGICAL MONITORING 43
9.0 RECOMMENDED PRECAUTIONS, CLASSIFICATION, AND SAFETY DATA 44
10.0 AVAILABILITY AND REFERENCE(S) FOR EXISTING REVIEW(S) 44

APPENDIX A 45

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH(CH_2\text{-}CH_3)\text{-}C(=O)\text{-}OH$
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5 STUDY	Info. Available Y/N	OECD Study Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degrability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5 STUDY	Info Available Y/N	OECD Summary Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

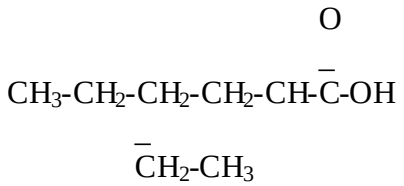
2.3 **Common Synonyms:**

a-Ethylcaproic acid
2-Ethylcaproic acid
a-Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**

$C_8H_{16}O_2$

* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **<u>Physical-Chemical Data</u>**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33×10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]

NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water** (Preferred Study)

log Pow = 3 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup [ ] open cup [X]

Method:

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 **pH in Water**

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES [ ]
NO [X]

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 **Other Data**

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 **Source of Exposure**

* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 **Other Remarks:**

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 **Environmental Fate and Pathways**

* 5.1 **Degradability (Biotic and Abiotic)**

5.1.1 **Biodegradability**

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic [ ]

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, J. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES [ ]
NO [X]

Test Results: BOD_5 = 60 % of Theoretical (2.44 g O_2/g test substance).
BOD_{10} = 76 % of Theoretical (2.44 g O_2/g test substance).
BOD_{20} = 83 % of Theoretical (2.44 g O_2/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 **Sewage Treatment**

Comments: No Data Available.

5.1.3 **Stability in Air** (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES [ ]

NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 **Stability in Water** (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES [ ]
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 **Identification of Main Mode of Degradability in Actual Use**

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES [ ]
NO [X]

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 <u>Ecotoxicological Data</u>

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static [X], semi-static [ ], flow-through [ ]
Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test Results: LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Daphnia magna (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES [ ]
NO [X]

Test Results: 48 hr EC_{50} = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC_0 = 62.5 mg/L, 48 hr EC_{100} = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC_0 - highest tested concentration without effect after 48 hours. EC_{100} - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengessellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES [ ]
NO [X]

Test Results: 72 hr EbC_{10} = 32.543 mg/L
72 hr EbC_{50} = 60.511 mg/L

96 hr EbC_{10} = 24.496 mg/L
96 hr EbC_{50} = 40.616 mg/L

72 hr EuC_{10} = 31.940 mg/L
72 hr EuC_{50} = 49.279 mg/L

96 hr EuC_{10} = 27.938 mg/L
96 hr EuC_{50} = 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

6.5 **Toxicity to Bacteria**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.6 **Toxicity to Terrestrial Organisms**

6.6.1 **Toxicity to Soil Dwelling Organisms**

Test Results: No Data Available.

6.6.2 **Toxicity to Plants**

Test Results: No Data Available.

6.6.3 **Toxicity to Birds**

Test Results: No Data Available.

6.7 **Biological Effects Monitoring (Including Biomagnification)**

Test Results: No Data Available.

6.8 **Biotransformation and Kinetics in Environmental Species**

No Data Available.

7.0 **<u>Toxicological Data</u>** (oral, dermal and inhalation, as appropriate)

* 7.1 **Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES [ ]
NO [X]

Test Results: Discriminating dose (for fixed dose only): LD_{50} = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES [X]
NO [ ]

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 **Acute Dermal Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES [ ]
NO [X]

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance**: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES [X]
NO [ ]

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 Eye Irritation

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES [ ]

NO [X]

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

7.3 Skin Sensitisation

Test Substance:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES [ ]
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES [ ]
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. Toxicol. Lett. 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed

consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized in extremis. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]

NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-

dose groups, respectively. One male from the mid-dose group was found dead during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and

mid-dose groups. Absolute and relative (to body weight) liver weight were significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes),

but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with

the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 Genetic Toxicity

7.5.1 Bacterial test

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: S. typhimurium TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES [ ]

NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES [ ]

NO [ ]

Test Results: No Data Available.

Comments:

Reference:

7.5.3 **Non-Bacterial Test *In Vivo***

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

GLP: YES [X]
NO [ ]

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

Comments: 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. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 **Carcinogenicity**

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.7 Reproductive and Developmental Toxicity

7.7.1 Reproductive Toxicity

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]
NO [X]

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were

comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and Postnatal Development in Wistar Rats. Fundam. Appl. Toxicol. in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [ ]
NO [X]

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethyhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratol. 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES [ ]
NO [X]

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryolethality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryolethality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. Life Sci. 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES [ ]
NO [X]

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs

was significantly higher in the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in .the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. Fundam. Appl. Toxicol. 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrlBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour preiod; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

GLP: YES [ ]
NO [X]

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage of resorptions increased at higher dose levels, and was also high in the

animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. Toxicol. Appl. Pharmacol. 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose

group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]

NO [ ]

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption

by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(G.) **Teratogenicity/Developmental toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days (GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into three groups and fed diets as described for the second experiment. The

animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg)was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. Teratology 53(2):p88, Abstract 21.

7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

7.9 Toxicodynamics, Toxico-Kinetics

Test Substance: [2-^{14}C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmole) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO [ ]

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid

		7% unmetabolized 2-Ethylhexanoic acid
Oral	***100 mg/kg***	***12% glucuronide-2-Ethylhexanoic acid***
	(Repeated)	12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 **Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m^3 (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of

approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid elimination of the material. No urine samples were collected during the work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be 2-2.33 x 10^{-4} mg/kilogram body weight/8 hour workday. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. Int. Arch. Occup. Environ. Health, 62:213-216.

9.0 Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 Availability and Reference(s) for Existing Review(s)

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

Note: Appendix I is Robust Summaries and SIDS Dossier for 2-ethylhexanoic acid.

1.0 SUBSTANCE INFORMATION

Generic Name	:	Hexanoic acid, 2-ethyl, tin salt
Chemical Name	:	Hexanoic acid, 2-ethyl, tin salt
CAS Registry No.	:	310-10-0
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$C_{16}H_{30}O_4Sn$
Molecular Weight	:	405.1006
Synonyms and Trade names	:	Tin 2-ethylhexanoate; ethylhexanoic acid tin(2+) salt; stannous ethylhexanoate; tin(II) 2-ethylhexanoate; stannous octoate
References	:	http://www.chemfinder.com

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Melting point is reported as –118.4°C for 2-ethylhexanoic acid (See Appendix I: 3.1
Reliability :
Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Boiling point is reported as 227.6°C for 2-ethylhexanoic acid (See Appendix I.: 3.2)
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value : at °C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference

2.4 VAPOR PRESSURE

Type :

Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Vapor pressure is reported as 1.33 x 10^{-3} kPa at 20°C for 2-ethylhexanoic acid (See Appendix I: 3.3)
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The log partition coefficient (log Kow) for 2-ethylhexanoic acid was estimated to be 3.0 (See Appendix I: 3.4).
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The water solubility of 2-ethylhexanoic acid was reported to be 25

mg/L at 25°C (See Appendix I: 3.5).

Reliability :

Reference :

2.7 FLASH POINT

Type :

Guideline/method :

Value : °C

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark : **Supporting data for dissociation products:**
Acid: A flashpoint of 118°C was reported for 2-ethylhexanoic acid (See Appendix I: 3.6).

Reliability :

Reference :

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	5.09 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Stannous 2-ethylhexanoate, lot number 71K0082, received from Aldrich Chemical Company. Hazy yellow liquid, purity of 95%
Approximate water solubility	:	100 mg/L as determined visually in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of stannous 2-ethylhexanoate were prepared at a nominal concentration of 50 mg/L by fortification of degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.001N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKa value was 5.09 (SD = 0.0337) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at

environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of stannous 2-ethylhexanoate, Wildlife International, Ltd. Study No. 534C-106, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %

%

Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Aerobic biodegradation of 2-ethylhexanoic acid was reported with BOD_5, BOD_{10} and BOD_{20} at 60%, 76% and 83% of Theoretical (2.44 g oxygen /g test substance). (See Appendix I: 5.1.1).
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h LC50 for fathead minnows (*Pimephales promelas*) is reported as 70 mg/L at a pH of 5.3 – 5.5 for 2-ethylhexanoic acid (See Appendix I: 6.1.1). **Metal:** The reported 96-h LC50 for tin chloride to the mud dab (*Limanda limanda*) was greater than 0.035 mg Sn/L (ECOTOX database, 2002). In a 28-day renewal exposure of rainbow trout (*Oncorhynchus mykiss*) to tin chloride, the LC50 was determined to be 0.4 mg Sn/L. (ECOTOX database, 2002).
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:**

Acid: The 48-h EC50 for *Daphnia magna* for 2-ethylhexanoic acid was reported to be 85.38 mg/L (95% CI: 79.77 – 91.38 mg/L), classified as slightly toxic. (See Appendix I: 6.2.1).
Metal: Reported 48-h EC50 values for tin chloride for *Daphnia magna* include 19.5 mg Sn/L and 55 mg Sn/L (ECOTOX database, 2002). In a 21-day chronic renewal exposure of *Daphnia magna* to tin chloride, the EC50 was determined to be 42 mg Sn/L based upon immobility and 1.5 mg Sn/L based upon reproduction. (ECOTOX database, 2002).

Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The 96-h E_bC50 (EC50 based upon biomass) for the green alga *Scenedesmus subspicatus* was reported to be 40.616 mg/L for 2-ethylhexanoic acid (See Appendix I: 6.3).
Metal: Reported 72-h EC50 values for tin chloride for *Skeletonema costatum* range from 0.21 mg Sn/L to greater than 0.5 mg Sn/L. For an 8-day exposure of *Ankistrodesmus falcatus* to tin chloride, the reported EC50 was 12 mg Sn/L. (ECOTOX database, 2002).
Reliability :
Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:
Type	:
Guideline/method	:
Species	:
Number of animals	:
Males	:
Females	:
Doses	:
Males	:
Females	:
Vehicle	:
Route of administration	:
Exposure time	:
Product type guidance	:
Decision on results on acute tox. tests	:
Adverse effects on prolonged exposure	:
Half-lives	: 1st: 2nd: 3rd:
Toxic behavior	:
Deg. product	:
Deg. products CAS#	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:

Acid: Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days as oral unlabeled at 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid
		7% glucuronide-diacid or hydroxylated 2- Ethylhexanoic acid
		2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg	20% glucuronide-2-Ethylhexanoic acid
	(Single)	14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		7% unmetabolized 2-Ethylhexanoic acid
Oral	100 mg/kg (Repeated)	12% glucuronide-2-Ethylhexanoic acid
		12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid
		3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
		3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic

acid

9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid
2% unmetabolized 2-Ethylhexanoic acid

Metal: Inorganic tin compounds are not readily absorbed after oral or inhalation exposure and show only limited effects after dermal exposure. At 48 hours after oral administration of ^{113}Sn, approximately 95% or more of the administered radioactivity was recovered in the feces with 1% or less in the urine. The various forms of tin (^{113}Sn) compounds administered were stannous pyrophosphate, stannous fluoride, stannic fluoride, stannous citrate, and stannic citrate. The absorption of Sn(II) from the gastrointestinal tract was reported to be 2.85% in rats. Several studies support the finding of low accumulation of tin in body tissues, including bone, liver and kidneys. At 48 hours after oral administration of 20 mg tin/kg/day (as Sn(II) citrate) in rats, the percentages of the dosed tin detected were 1.02% in the skeleton, 0.08% in the liver, and 0.09% in the kidneys. The half-life of Sn(II) was reported to be 10–20 days in the liver and kidney and 20-40 days in bone. After exposure to high dose levels, tin has been detected in blood and brain tissue. Tin does not appear to readily cross the placenta. (ATSDR Toxicological Profile for Tin and Compounds, 1992). Absorbed inorganic tin is mainly excreted in the urine. (WHO, 1980, Environmental Health Criteria 15, Tin and Organotin Compounds).

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type	:	Acute Oral (LD50) Toxicity
Guideline/Method	:	
Species	:	Rat
Strain	:	Sprague-Dawley, albino
Sex	:	Male, young adults
Number of animals	:	4 groups of 5 each
Vehicle	:	
Doses	:	1.6, 3.2, 6.4 and 12.8 g/kg. No controls were included.
LD50	:	5.87 g/kg (95% CI: 3.14 – 10.98 g/kg).
Year	:	1967
GLP	:	No
Test substance	:	Stannous octoate. No further information provided.
Method	:	
Method detail	:	Animals (200 - 250 g) fasted 24 hours prior to dosing. Administered the test material (as supplied) via intragastric intubation. Observed for 21-days post-exposure.
Result	:	LD50 5.87 g/kg (95% CI: 3.14 – 10.98 g/kg). Rats receiving the two highest doses were listless following test material administration. Fatalities (3/5 and 4/5 at 6.4 and 12.8 g/kg, respectively) occurred within first four days at these two dose levels, with one fatality at 3.2 g/kg on day 12.
Remark	:	**Supporting data for dissociation products:** **Acid:** The LD50 for rats for 2-ethylhexanoic acid was reported to be 1600 – 3200 mg/kg as determined via gavage. (See Appendix I: 7.1.1). **Metal:** Inorganic tin and its salts are not highly toxic, mainly because of their poor absorption and rapid tissue turnover. The systemic toxicity of simple tin salts is difficult to assess because of the irritant properties of their solutions. (WHO, 1980, Environmental Health Criteria 15, Tin and Organotin Compounds). The lowest oral dose that produced death following a single

Compounds). The lowest oral dose that produced death following a single gavage administration of stannous chloride was 473 mg Sn/kg bw in rats and 378 mg Sn/kg bw in mice. In dietary feeding studies using stannous chloride, survival was complete for rats fed up to 945 mg Sn/kg/d and mice fed up to 2457 mg Sn/kg/d for 14 days. (ATSDR Toxicological Profile for Tin and Compounds, 1992).

Reliability : [2] Reliable with restriction. Very brief description of methods and results. Characterization of test material absent. No pathology conducted.

Reference : AME Associates (1967). Acute oral toxicity study in rats with stannous octoate. Conducted for M&T Chemicals, Inc., Rahway, NJ

Type : Acute Oral (LD50) Toxicity
Guideline/Method :
Species : Rat
Strain :
Sex : Male
Number of animals : 6 per dose
Vehicle : Paraffin oil
Doses : 1.0, 1.7, 2.89, 4.91, and 8,35 g/kg. Dose volume 10 ml/kg.
LD50 : 3.4 g/kg (95% CI: 2.5 – 4.8 g/kg)
Year : 1980
GLP : Not reported
Test substance : Stannous octoate. No further information provided.
Method :
Method detail : Test material administered by gavage. Observed animals for 14-days post-exposure, sacrificed and gross pathology observed.
Result : Death occurred within 1 to 2 days after dosing. Mortalities were 0/6, 0/6, 3/6, 4/6 and 6/6 at the five dose levels. LD50 3.4 g/kg (95% CI: 2.5 – 4.8 g/kg). Clinincal signs of toxicity included piloerection, soiled coat, hypokinesis and ataxia. No clinical signs persisted after 11 days. Postmortem observations revealed fluid gut contents, pale kidneys, mottled liver and patchy pink lung. Study performed by Inveresk Research International, Edinburgh, Scotland.
Remark :
Reliability : [2] Reliable with restriction. Very brief description of methods and results. Characterization of test material absent.
Reference : U.S. EPA/OPTS Public Files. Initial submission: data from toxicity study with stannous octoate in mice with cover letter dated 051492. Available from National Technical Information Service as Fiche # OTS0539764. Produced 06/07/88; received 05/29/92.

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :

Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The LC50 was greater than 2.36 mg/L (400 ppm) for rats exposed to 2-ethylhexanoic acid for 6 hours (See Appendix I: 7.1.2).
Metal: Intratracheal administration of 50 mg of metallic tin dust to rats was well tolerated and no fibrosis was produced within one year of exposure. Exposure of guinea pigs by inhalation to tin (IV) chloride (3 mg/L for 10 minutes daily for several months) produced only transient irritation of the nose and eyes. (WHO, 1980, Environmental Health Criteria 15, Tin and Organotin Compounds).
Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The dermal LD50 for guinea pigs for 2-ethylhexanoic acid (undiluted) was reported to be < 5.0 mL/kg, as both animals receiving this dose died. No mortality was seen in animals receiving the test substance as a 20% preparation in 90% acetone/10% corn oil at 5, 10 and 20 mL/kg.(See Appendix I: 7.1.3).
Metal: No data.
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type : Draize skin irritation
Guideline/method :
Species : Rabbit
Strain : Albino
Sex : Male and female
Concentration :
Exposure :
Exposure time : 24 h
Number of animals : Six, three male and three female
Vehicle :

Classification	:	Mild irritant
Year	:	1967
GLP	:	No
Test substance	:	Stannous octoate. No further information provided.
Method	:	
Method detail	:	The hair was clipped on the back and two areas approx. 10 cm apart were selected as application sites. One site was abraded by making four epidermal incisions in a cross hatch pattern. 0.5 mL of test material was applied to each site and covered with gauze. The trunk was then wrapped in polyethylene sheeting and taped. The test material was left in contact with the skin for 24 h, at which time the trunk bands were removed. The sites were examined 24 h and 72 h after application. The scoring method was that of Draize, Woodard and Calvery.
Result	:	The average score for erythema and eschar formation at 24 h was 1.50 for intact skin and 1.33 for abraded skin. For edema formation at 24 h, the average score was 1.33 for intact skin and 1.50 for abraded skin. At 72 h, the average scores ranged from 0 to 0.17. The primary irritation score was 1.54. At the 72 hour scoring, almost no irritation was noted in any animal.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced slight necrosis in 5 of 6 animals (New Zealand white rabbits) after 4 hours with subsequent eschar formation (slight to moderate). (See Appendix 1: 7.2.1(B)). **Metal:** Stannous fluoride (0.25%) and stannous chloride (1%) applied to abraded rabbit skin produced intraepidermal pustules with complete destruction of the epidermis but the stratum corneum remained intact. No injury occurred when the solutions were applied to intact skin (WHO, 1980, Environmental Health Criteria 15, Tin and Organotin Compounds).
Reliability	:	[2] Reliable with restriction. Very brief description of methods and results. Characterization of test material absent and test material concentration not reported.
Reference	:	AME Associates (1967). Evaluation of stannous octoate by Draize skin irritation technique. Conducted for M&T Chemicals, Inc., Rahway, NJ

Type	:	Skin irritation and acute percutaneous absorption
Guideline/method	:	
Species	:	Rabbit
Strain	:	New Zealand White rabbits
Sex	:	Female
Concentration	:	2000 mg/kg
Exposure	:	
Exposure time	:	Prolonged contact (24 h) and repeated applications
Number of animals	:	Two
Vehicle	:	
Classification	:	
Year	:	1988
GLP	:	Not reported
Test substance	:	Stannous octoate, also known as Fomrez C-2.Pale yellow liquid.
Method	:	
Method detail	:	Test material was topically applied to intact and abraded skin at 3 sites. The confined sites on the abdomen received 3 (abraded skin) or 5 (intact skin) 0.5 mL applications. The unconfined site, located on the right ear pinna, received five 0.5 mL applications.
Result	:	Prolonged contact and repeated applications both resulted in slight erythema to all three sites. The test material is not likely to be absorbed through the skin in acutely toxic amounts. Both rabbits appeared healthy.

Remark	:	
Reliability	:	
Reference	:	U.S. EPA/OPTS Public Files. Initial submission: Fomrez C-2: acute toxicological properties study with cover sheet and letter dated 04/30/91(sanitized). Available from National Technical Information Service as Fiche # OTS0536498. Produced 10/24/88; received 05/12/92.
Type	:	Skin sensitization
Guideline/method	:	OECD Guideline 406, “Skin Sensitization”, EEC Directive 84/449/EEC Part 6B, and Magnusson and Klingman, 1970.
Species	:	Guinea pig
Strain	:	Himalayan, albino
Sex	:	Female; approx. 9 weeks old, 344 – 465 g
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	5 in preliminary study; 20 in experimental group, 10 in control group
Vehicle	:	
Classification	:	
Year	:	1992
GLP	:	Yes
Test substance	:	Stannous octoate, also known as DABCO T-9. Lot no. 9H114551, clear yellow liquid. Purity not reported, treated as 100%. Prepared in propylene glycol
Method	:	OECD Guideline 406, “Skin Sensitization”, EEC Directive 84/449/EEC Part 6B, and Magnusson and Klingman, 1970.
Method detail	:	In the primary irritation experiments, four intradermal injections (0.1 mL/site) were made into the clipped shoulder region of one guinea pig at a concentration of 5% (w/w) of the test substance in propylene glycol. The resulting dermal reactions were assessed 24 and 48 hours later. In addition, the animal was also treated epidermally at the shaved left flank with 0.5 mL of the undiluted test substance. Four other animals were shaved on the left flank and exposed to 0.05 mL of 100%, 50%, 25%, and 10% (w/w) test substance concentration in propylene glycol, occlusively administered for 24 hours. After 24 hours, the dressings and residual test article were removed. The treated skin was evaluated 24 and 48 hours after bandage removal. In the main study, intradermal injections were made for induction purposes. Three pairs of injections (0.1 mL/site) were made using (1) test substance diluted to 2% (w/w) with propylene glycol; (2) Freunds’ Complete Adjuvant:distilled water (50:50); and (3) test substance at 4% emulsified in 50:50 Freunds’ Complete Adjuvant. Seven days after the intradermal injections, the scapular area was shaved and the test substance (0.5 mL of 50% in propylene glycol) applied epidermally. After 48 hours, the dressings and residual test material were removed. Reaction sites were assessed for erythema and oedema immediately after removal of the dressings. Test and control guinea pigs were challenged two weeks after the epidermal application. This was done using 0.05 mL of each of the following, applied to the shaved left flank using Square chambers attached to Micropore tape: 10%, 5%, and 2% (w/w) in propylene glycol, and propylene glycol control. Dressings and residual test substance were removed after 24 hours. Sites were assessed for redness and swelling 24 and 48 hours after removal using a numerical grading system.
Result	:	No signs of systemic toxicity were observed and no mortality occurred. After the 48 hours occluded epidermal induction exposure, the experimental animals showed slight to severe erythema and slight to well-defined

		animals showed slight to severe erythema and slight to well-defined oedema. In the challenge test, 17, 16 and 13 animals showed a skin reaction in response to 10%, 5% and 2% test substance concentrations, respectively. These results led to a sensitization rate of 85%. Considered to have extreme sensitizing properties.
Remark	:	
Reliability	:	[1] Reliable without restriction. Guideline study conducted under GLP.
Reference	:	U.S. EPA/OPTS Public Files. Initial submission: Report on the assessment of contact hypersensitivity to DABCO T-9 in the albino guinea pig (maximization test) with attachments and cover letter dated 02/28/92. Available from National Technical Information Service as Fiche # OTS0536069. Produced 1/02/92; received 03/10/92.

Additional references for skin irritation: In a contact dermal irritation/skin sensitization study with guinea pigs, following the Modified Buehler method, stannous octoate (as known as Fomrez C-2) caused delayed contact hypersensitivity, with 6/10 treated animals showing slight to moderate erythema. [U.S. EPA/OPTS Public Files. Initial submission: Fomrez C-2: acute toxicological properties study with cover sheet and letter dated 04/30/91(sanitized). Available from National Technical Information Service as Fiche # OTS0536498. Produced 10/24/88; received 05/12/92].

5.2.2 EYE IRRITATION

Type	:	
Guideline/method	:	
Species	:	Rabbit
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	Stannous octoate, undiluted and as 1% in propylene glycol
Method	:	
Method detail	:	
Result	:	Moderate eye irritant. The undiluted material caused moderate conjunctivitis and swelling accompanied by slight to moderate corneal injury which did not subside in one week. The material tested as 1% in propylene glycol caused slight pain and conjuncitivitis which subsided in one week.
Remark	:	**Supporting data for dissociation products:** **Acid:** 2-ethylhexanoic acid produced severe corneal irritation in rabbits after 24 hours (See Appendix I: 7.2.2; note study was of low reliability). **Metal:** Transient irritation of the eyes was produced by exposure of guinea pigs by inhalation to tin (IV) chloride (3 mg/L for 10 minutes daily for several months). (WHO, 1980, Environmental Health Criteria 15, Tin and Organotin Compounds).
Reliability	:	[3] Not reliable. Documentation insufficient for assessment.
Reference	:	U.S. EPA/OPTS Public Files. Initial submission: data from toxicity study with stannous octoate in mice with cover letter dated 051492. Available from National Technical Information Service as Fiche # OTS0539764. Produced 06/07/88; received 05/29/92.

5.4 REPEATED DOSE TOXICITY

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Number of animals	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Post exposure period	:
Doses	:
Control group	:
NOAEL	:
LOAEL	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: Rats were fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups and allowed 28 days of recovery.

Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs

(kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group.

All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day) (See Appendix I: 7.4(H)). These data are consistent with four previous repeated dose studies in Fischer rats (See Appendix I: 7.4).

Metal: Soluble tin salts are gastric irritants; however the concentrations required to elicit an acute gastrointestinal reaction have not been determined reliably (WHO, 1980, Environmental Health Criteria 15, Tin and Organotin Compounds). In rats fed stannous chloride over a 13 week period, 4 of 10 animals receiving 315 mg Sn/kg/d died. Based upon the most sensitive effects in this study (hematologic, hepatic, and body weight gain), the NOAEL was 32 mg Sn/kg/d and the LOAEL was 95 mg Sn/kg/d. The NOAEL for mice fed stannous chloride over a 13 week period was reported to be 157 mg Sn/kg/d based upon gastrointestinal effects. Long-term feeding studies (105 weeks) using stannous chloride identified a NOAEL of 63 mg Sn/k/d for the rat and 164 mg Sn/kg/d for the mouse. (ATSDR Toxicological Profile for Tin and Compounds, 1992).

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Mutagenicity
Guideline/method :
System of testing : Ames assay
Species : *Salmonella typhimurium*
Strain : TA98, TA100, TA1535, TA1537 and TA1538
Test concentrations : 0.5 to 500 µg/plate. Dissolved in DMSO.
Cytotoxic concentr. :
Metabolic activation : Conducted both with and without activation. No further details.
Year : 1980
GLP : Not reported
Test substance : Stannous octoate
Method :
Method detail : A Spot Plate Test against each indicator organism was also conducted on the undiluted test material. No further details provided. Study conducted at Dow Corning Corporation, Toxicology Department.
Result : Negative. No evidence of genetic activity.
Remark : **Supporting data for dissociation products:**
Acid: In the Ames assay, no mutagenic activity was observed with 2-ethylhexanoic acid, either with or without activation (See Appendix I: 7.5.1).
Metal: Stannous chloride was not genetically active *in vitro* with *Salmonella* strains TA-1530 and G-46 and *Saccharomyces* strain D3. In addition, according to the *in vitro* cytogenetics test, stannous chloride produced no significant aberrations in chromosomes of human tissue culture cells. (Litton

significant aberrations in chromosomes of human tissue culture cells. (Litton Bionetics, Inc., 1974, Mutagenic evaluation of Compound FDA 71-33, Stannous Chloride. Prepared for the Food and Drug Administration, NTIS PB-245 461). Negative results with stannous chloride were observed in the Rec-assay with *Bacillus subtilis;* however, DNA damage was noted with mammalian cells treated with stannous chloride, and cytogenetic studies also gave positive results with stannous chloride for chromosomal aberrations and sister chromatid exchanges. (ATSDR Toxicological Profile for Tin and Compounds, 1992).

Reliability : [4] Not assignable. Documentation insufficient for assessment.

Reference : U.S. EPA/OPTS Public Files. Initial submission: data from toxicity study with stannous octoate in mice with cover letter dated 051492. Available from National Technical Information Service as Fiche # OTS0539764. Produced 06/07/88; received 05/29/92.

Type : Cytotoxicity

Guideline/method :

System of testing : L929 Mouse fibroblast culture

Species :

Strain :

Test concentrations : 8 ug – 1 mg

Cytotoxic concentr. :

Metabolic activation :

Year : 1973

GLP : Not reported

Test substance : Stannous octoate

Method :

Method detail : Test samples were prepared using stannous octoate in acetone or chloroform, which was spotted onto filter papers, allowed to evaporate, and irradiated with a Cobalt 60 source to give a radiation dose of 2.5 mega rads. To prepare the cell monolayers, 5 mL samples of mouse fibroblast cells were suspended in growth medium and pipetted into petri dishes to produce an initial cell concentration of 1 x 10^6. Incubation was at 36ºC for 24 hours. The stannous octoate samples were placed in contact with the cell monolayers and incubated for 48 hours. Dead cells were stained with 0.5% tryptan blue vital stain in phosphate buffered saline solution. Polyethylene and polyvinyl chloride were used as the nontoxic and toxic controls, respectively. Performed at St. Luke's Hospital, Bradford Yorkshire, UK

Result : No toxic effects at any test concentration

Remark :

Reliability : [4] Not assignable. Documentation insufficient for assessment.

Reference : U.S. EPA/OPTS Public Files. Initial submission: data from toxicity study with stannous octoate in mice with cover letter dated 051492. Available from National Technical Information Service as Fiche # OTS0539764. Produced 06/07/88; received 05/29/92.

5.6 GENETIC TOXICITY 'IN VIVO'

Type :

Guideline/method :

Species :

Strain :

Sex :

Route of admin. :

Exposure period :

Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 2-ethylhexanol in corn oil was negative in the mouse micronucleus test. (Since 2-ethylhexanol metabolizes to 2-ethylhexanoic acid, this study is relevant to 2-ethylhexanoic acid). (See Appendix I: 7.5.3)
Metal: Stannous chloride was not genetically active in the host-mediated assay with *Salmonella* strains TA-1530 and G-46 and *Saccharomyces* strain D3. Stannous chloride produced no detectable significant aberration of the bone marrow metaphase chromosomes of rats when administered orally. In addition, stannous chloride was considered to be non-mutagenic in rats in the Dominant Lethal Assay. (Litton Bionetics, Inc., 1974, Mutagenic evaluation of Compound FDA 71-33, Stannous Chloride. Prepared for the Food and Drug Administration, NTIS PB-245 461). Stannous chloride did not induce sex-linked recessive lethal mutations in germ cells of *Drosophila melanogaster* (Foureman, P., Mason, J.M., Valencia, R., and Zimmering, S., 1994. Chemical mutagenesis testing in *Drosophila*. X. Results of 70 coded chemicals tested for the National Toxicology Program, Environmental and Molecular Mutagenesis 23:208-227.)
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Several Teratogenicity/Developmental Toxicity Studies have been conducted with 2-ethylhexanoic acid (See Appendix I: 7.7.2). In the most reliable study, the NOEL for teratogenic

and developmental effects in rats for was 100 mg/kg/day; the NOEL for maternal effects was 250 mg/kg/day. For rabbits, these values were 250 mg/kg for offspring and 25 mg/kg for maternal animals. Details of this study are as follows.

Twenty-five pregnant Fischer 344 rats per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs. 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

For New Zealand white rabbits, fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights

were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

(See Appendix I: 7.2.2 (E and F)

Metal: Inorganic tin compounds have not been shown to be fetotoxic. No effects were seen in the fetuses of rats given sodium pentafluorostannite, sodium pentachlorostannite, and tin (II) fluoride. (WHO, 1980, Environmental Health Criteria 15, Tin and Organotin Compounds). The administration of up to 41.5 mg/kg body weight of stannous chloride to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities in soft or skeletal tissue was also unaffected. (Food and Drug Research Labs, Inc., 1974, Teratologic Evaluation of Compound FDA 71-33, Stannous Chloride, in Rabbits. Prepared for US Food and Drug Administration, PB-267-192). The administration of up to 50 mg/kg bw of stannous chloride to pregnant mice and rats for 10 consecutive days, and to pregnant hamsters for 5 consecutive days, had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities in soft or skeletal tissue was also unaffected. (Food and Drug Research Labs, Inc., 1972, Teratologic Evaluation of FDA 71-33, Stannous Chloride, in Mice, Rats and Hamsters. Prepared for US Food and Drug Administration, PB-221-780).

Reliability :

Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type	:
Guideline/method	:
In vitro/in vivo	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Duration of test	:
Doses	:
Control group	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: A One-Generation Reproduction Toxicity Study was conducted with 2-ethylhexanoic acid. Male and female Wistar rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains

Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

(See Appendix I: 7.7.1)

Metal: Tin(II) chloride was reported to cause testicular degeneration in rats after prolonged feeding (1.5 to 9.2 mg Sn/kg/d for 13 weeks). Histopathological degeneration was seen in a few animals who were treated for 9 weeks at 30.5 mg Sn/kg/d and then sacrificed because of their moribund physiological state. (ATSDR Toxicological Profile for Tin and Compounds, 1992).

Reliability :
Reference :

13.0 OTHER INFORMATION

13.1 CARCINOGENICITY

Type :
Guideline/method :
Species : Rat
Strain : Inbred August hooded
Sex : Males and females
Number of animals : 37 (17 males and 20 females) in exposed group, 40 animals (20 males and 20 females) in control group.
Route of admin. : Oral (through diet)
Exposure period : During weeks 0 – 8, fed 1% stannous 2-ethyl hexoate, followed by 4 weeks without exposure, then exposed during weeks 12 - 80 to 0.5% stannous 2-ethyl hexoate

Frequency of treatment	:	Food provided daily except Sundays
Duration of test	:	80 weeks
Doses	:	1% stannous 2-ethyl hexoate, containing 4500 ppm Sn (weeks 0 –8); 0.5% stannous 2-ethyl hexoate, containing 2250 ppm Sn (weeks 12 – 80). (This study also included a group of animals treated with 2% sodium chlorostannate; see Remarks).
Control group	:	Untreated feed (20% protein diet)
Year	:	1964
GLP	:	No
Test substance	:	Stannous 2-ethyl hexoate, dissolved in arachis oil and then mixed into powered feed (20% protein diet).
Method	:	
Method detail	:	Mothers were exposed beginning on the day their litters were born. After weaning, the young were segregated by sex, then fed the same diets as the mothers. After 8 weeks of exposure, the treated group was severely underweight and anemic. Due to this, the treatment was discontinued and the animals given control feed for 4 weeks, at which time their condition was greatly improved and body weights were comparable to the controls. Thus, at 12 weeks, exposure was resumed but at half the previous dose. The animals remained on this diet until death.
Result	:	Mortality in the stannous 2-ethyl hexoate treated group was 6/17 males and 4/20 females by 52 weeks and 11/17 males and 6/20 females by 80 weeks. Control mortality was 4/20 males and 3/20 females at 52 weeks; 8/20 males and 4/20 females at 80 weeks. Chronic respiratory disease was evident in the majority of animals (treated and controls) at 52 weeks and until the end of the study, but this was judged to not be a factor for carcinogenicity. Slight degenerative changes were observed microscopically in the livers of control as well as treated animals, as were areas of dilated tubules in the renal cortices of a few rats in each group. No hyperplastic or neoplastic lesions were seen in the gastrointestinal tract. There were no other significant pathological findings.
Remark	:	**Supporting data for dissociation products:** **Acid:** No data **Metal:** The Roe et al. (1965) study also evaluated the carcinogenic potential of sodium chlorostannate in rats. Three malignant tumors were seen in 30 rats which survived for 1 year or more on a diet containing 2% sodium chlorostannate (5000 ppm Sn). This was judged to be without significance. This study is regarded as flawed due to the development of pneumonia in most of the animals and the irregular dosing used. A bioassay in male and female rats and mice was conducted by the National Toxicology Program using diets containing 32 or 62 mg Sn/kg/d (for rats) and 82 or 164 mg Sn/kg/d (mice) for 105 weeks. The authors concluded that the incidence of tumors was not clearly related to the administration of stannous chloride. (ATSDR Toxicological Profile for Tin and Compounds, 1992). Administration of tin(II) chloride to rats and mice at 5 mg Sn/L in drinking water throughout their lifetime did not produce any increase in incidence of tumors. (WHO, 1980, Environmental Health Criteria 15, Tin and Organotin Compounds).
Reliability	:	[2] Not reliable. Irregular dosing schedule used. Respiratory disease occurred in all animals, but was believed not to have interfered with carcinogenicity.
Reference	:	Roe, F.J.C., E. Boyland and K. Millican. 1965. Effects of oral administration of two tin compounds to rats over prolonged periods. Fd. Cosmet. Toxicol. 3: 277-280.

6.2 Other information

A tissue cell culture study was conducted with stannous octoate ("Catalyst M") to determine the cytopathic effects of the material or its extracts in contact with monolayers of diploid human cells. The test substance was applied to a sterile filter pad and the pad placed on confluent monolayers of human embryonic or fetal cells. In addition, the test substance was extracted in dimethylsulfoxide (DMSO) and in tissue culture medium (MEM) and the extracts placed on the monolayers. The test substance was cytotoxic in direct contact and the MEM extract also caused morphological changes. The DMSO extract caused no effects at the concentration tested. The MEM extract was quite acidic. [U.S. EPA/OPTS Public Files. Tissue cell culture studies comparative cytotoxicity of catalyst M and Catalyst I, with cover letter dated 4/20/94. Available from National Technical Information Service as Fiche # OTS0558183. Produced 04/01/86; received 04/28/94.]

APPENDIX I

ROBUST SUMMARIES
and
SIDS DOSSIER for:
2-Ethylhexanoic Acid

.....

CAS No. 149-57-5

Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

		Page
SIDS PROFILE		1
SIDS SUMMARY		2
1.0	GENERAL INFORMATION	4
2.0	CHEMICAL IDENTITY	4
	*2.1 CAS NUMBER	4
	*2.2 NAME	4
	2.3 COMMON SYNONYMS	4
	2.4 EMPIRICAL FORMULA	5
	*2.5 STRUCTURAL FORMULA	5
	2.6 PURITY OF INDUSTRIAL PRODUCT	5
	2.6.1 DEGREE OF PURITY	5
	2.6.2 IDENTITY OF MAJOR IMPURITIES	5
	2.6.3 ESSENTIAL ADDITIVES	5
3.0	PHYSICAL-CHEMICAL DATA	5
	*3.1 MELTING OR DECOMPOSITION POINT	5
	*3.2 BOILING POINT	5
	*3.3 VAPOR PRESSURE	6
	*3.4 PARTITION COEFFICIENT N-OCTANOL/WATER	6
	*3.5 WATER SOLUBILITY	7
	3.6 FLASH POINT (LIQUIDS)	7
	3.7 FLAMMABILITY	7
	3.8 PH IN WATER	8
	3.9 OTHER DATA	8
4.0	SOURCE OF EXPOSURE	8
	*4.1 PRODUCTION LEVELS EXPRESSED AS TONNES PER ANNUM	8
	4.2 PROCESSES	8
	*4.3 INFORMATION CONCERNING USES	8
	4.4 OPTIONS FOR DISPOSAL	8
	4.5 OTHER REMARKS	9
5.0	ENVIRONMENTAL FATE AND PATHWAYS	9
	5.1 DEGRADABILITY (BIOTIC AND ABIOTIC)	9
	5.1.1 BIODEGRADABILITY	9
	5.1.2 SEWAGE TREATMENT	10
	5.1.3 STABILITY IN AIR	10
	5.1.4 STABILITY IN WATER	10
	5.1.5 IDENTIFICATIN OF MAIN MODE OF DEGRADABILITY IN ACTUAL USE	10
	5.2 BIOACCUMULATION	11
	5.3 TRANSPORT AND DISTRIBUTION BETWEEN ENVIRONMENTAL COMPARTMENTS	11
	5.4 MONITORING DATA	11
6.0	ECOTOXICOLOGICAL DATA	11
	6.1 TOXICITY TO FISH	11
	6.1.1 RESULTS OF ACUTE TESTS	11
	6.1.2 RESULTS OF LONG-TERM TESTS	12
	6.2 TOXICITY TO DAPHNIDS	13
	6.2.1 RESULTS OF ACUTE TESTS	13
	6.2.2 RESULTS OF LONG-TERM TESTS	13
	6.3 TOXICITY TO ALGAE	14
	6.4 TOXICITY TO OTHER AQUATIC ORGANISMS	14

Page

6.5 TOXICITY TO BACTERIA 15
*6.6 TOXICITY TO TERRESTRIAL ORGANISMS 15
6.6.1 TOXICITY TO SOIL DWELLING ORGANISMS 15
6.6.2 TOXICITY TO PLANTS 15
6.6.3 TOXICITY TO BIRDS 15
6.7 BIOLOGICAL EFFECTS MONITORING 15
6.8 BIOTRANSFORMATION AND KINETICS IN ENVIRONMENTAL SPECIES 15
7.0 TOXICOLOGICAL DATA 15
7.1 ACUTE TOXICITY 15
7.1.1 ACUTE ORAL TOXICITY 16
7.1.2 ACUTE INHALATION TOXICITY 17
7.1.3 ACUTE DERMAL TOXICITY 18
7.2 CORROSIVENESS/IRRITATION 19
7.2.1 SKIN IRRITATION 19
7.2.2 EYE IRRITATION 20
7.3 SKIN SENSITISATION 20
*7.4 REPEATED DOSE TOXICITY 21
*7.5 GENETIC TOXICITY 27
7.5.1 BACTERIAL TEST 27
7.5.2 NON-BACTERIAL IN VITRO TEST 28
7.5.3 NON-BACTERIAL TEST IN VIVO 29
7.6 CARCINOGENICITY 29
*7.7 REPRODUCTIVE AND DEVELOPMENTAL TOXICITY 30
7.7.1 REPRODUCTIVE TOXICITY 30
7.7.2 TERATOGENICITY/DEVELOPMENTAL TOXICITY 32
7.8 SPECIFIC TOXICITIES (NEURO TOXICITY, IMMUNOTOXICITY, ETC.) 41
7.9 TOXICODYNAMICS, TOXICO-KINETICS 41
8.0 EXPERIENCE WITH HUMAN EXPOSURE 43
8.1 BIOLOGICAL MONITORING 43
9.0 RECOMMENDED PRECAUTIONS, CLASSIFICATION, AND SAFETY DATA 44
10.0 AVAILABILITY AND REFERENCE(S) FOR EXISTING REVIEW(S) 44

APPENDIX A 45

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH(CH_2\text{-}CH_3)\text{-}C(=O)\text{-}OH$
	OTHER CHEMICAL IDENTITY INFORMATION	
3.0	SOURCES AND LEVELS OF EXPOSURE	No likely exposure of public because this material is used exclusively as an industrial intermediate. Minimal likelihood of dermal exposure to workers during processing.
3.1	PRODUCTION RANGE	5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).
3.3	CATEGORIES AND TYPES OF USE	2-Ethylhexanoic acid is categorized as an intermediate for industrial use (closed system). There is no public or export use.
Issues for discussion		

SIDS SUMMARY

CAS-Number 149-57-5 STUDY	Info. Available Y/N	OECD Study Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
PHYSICAL-CHEMICAL							
2.1 Melting Point	Y	N	N	Y	N	Y	N
2.2 Boiling Point	Y	N	N	Y	N	Y	N
2.3 Vapour Pressure	Y	N	N	Y	N	Y	N
2.4 Partition Coefficient	Y	N	N	N	Y	Y	N
2.5 Water Solubility	Y	N	N	Y	N	N	N
OTHER STUDIES RECEIVED	Y						
ENVIRONMENTAL FATE/BIODEGRADATION							
4.1.1 Aerobic Biodegradability	Y	N	N	Y	N	Y	N
4.1.3 Abiotic Degrability							
4.1.3.1 Hydrolysis	N	-	-	-	-	-	N
4.1.3.2 Photodegradability	N	-	-	-	Y	Y	N
4.3 Env. Fate/Distribution	N	-	-	-	-	-	N
Env. Concentration	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						
ECOTOXICOLOGY							
5.1 Acute Toxicity Fish	Y	N	N	Y	N	Y	N
5.2 Acute Toxicity Daphnia	Y	N	N	Y	-	Y	N
5.3 Acute Toxicity Algae	Y	N	N	Y	-	Y	N
5.6.1 Acute Toxicity Terrest. Organisms	N	-	-	-	-	-	N
5.6.2 Acute Toxicity Terrest. Plants	N	-	-	-	-	-	N
5.6.3 Acute Toxicity Avians	N	-	-	-	-	-	N
5.6.4 Avian Reproduction	N	-	-	-	-	-	N
OTHER STUDIES RECEIVED	N						

SIDS SUMMARY (Continued)

CAS No: 149-57-5 STUDY	Info Available Y/N	OECD Summary Y/N	GLP Y/N	Other Study Y/N	Estimation Method Y/N	Acceptable Y/N	Testing Required Y/N
TOXICOLOGY							
6.1 Acute Oral	Y	Y	N	Y	N	Y	N
Acute Dermal	Y	N	N	Y	N	N	Y
Acute Inhalation	Y	N	N	Y	N	N	N
6.4 Repeated Dose	Y	Y	Y	N	N	Y	N
6.5 Genetic Toxicity							
- Gene Mutation	Y	N	N	Y	N	Y	N
- Chromosome Aberration	Y	-	-	-	-	-	N
6.7 Reproductive Toxicity	Y	N	Y	-	-	Y	N
OTHER STUDIES RECEIVED	Y						

Summary of Responses to the OECD Request for
Available Data on HPV Chemicals

1.0 General Information

Name of Sponsor Country: United States of America

Contact Point:

Mr. Charles Auer
Director - Existing Chemicals Assessment Division
Office of Toxic Substances (TS-788)
U S Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
Telephone (202) 382-3442
Fax (202) 382-7883, -7884, -7885

Name of Lead Organization: US Environmental Protection Agency

2.0 Chemical Identity

* 2.1 **CAS Number:** 149-57-5

* 2.2 **Name** (Name Supplied by the OECD): 2-Ethylhexanoic acid

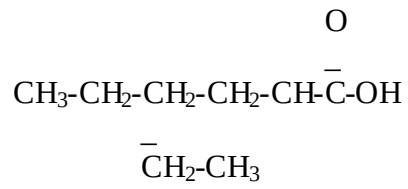
2.3 **Common Synonyms:**

a-Ethylcaproic acid
2-Ethylcaproic acid
a-Ethylhexanoic acid
Butylethylacetic acid
Ethylhexoic acid
2-EHA
2-EH acid
2-Ethylhexoic acid
2-Ethylhexanoic acid
2-Butylbutanoic acid
2-Heptanecarboxylic acid
3-Heptanecarbolic acid
Octanoic acid

2.4 **Empirical Formula:**

$C_8H_{16}O_2$

* 2.5 **Structural Formula:**



2.6 **Purity of Industrial Product**

2.6.1 **Degree of Purity** (Percentage by Weight/Volume): 99% by weight

2.6.2 **Identity of Major Impurities** (Typical Analysis): None detected.

2.6.3 **Essential Additives** (Stabilizing Agents, Inhibitors, Other Additives), if applicable: Not applicable.

3.0 **<u>Physical-Chemical Data</u>**

* 3.1 **Melting or Decomposition Point:** -118.4°C (melting point)

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.2 **Boiling Point** (Including Temperature of Decomposition, If Relevant): 227.6°C

Method: (e.g., OECD, Others): None provided.

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.3 **Vapor Pressure:**

1.33×10^{-3} kPa at 20°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]

NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

* 3.4 (A.) **Partition Coefficient n-Octanol/Water** (Preferred Study)

log Pow = 3 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Lyman, W.J., Reehl, W.F., and Rosenblatt, D.H. (1982). Handbook of Chemical Property Estimation Methods: Environmental Behavior of Organic Compounds, Chapter 1. McGraw-Hill, New York.

(B.) **Partition Coefficient n-Octanol/Water (Additional Information)**

log Pow = 2.64 at 25°C

Method: calculated [X]
measured [ ]

GLP: YES [ ]
NO [X]

Analytical Method: Estimated by the method of Hansch and Leo

Comments (e.g., is the compound surface active or dissociative?):

Reference: Pamona College Medicinal Chemistry Project, Claremont, CA

* 3.5 **Water Solubility:**

25 mg/L at 25°C

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Analytical Method: None provided.

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.6 **Flash Point (Liquids):** 118°C

closed cup [ ] open cup [X]

Method:

GLP: YES [ ]
NO [X]

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.7 **Flammability**

Method (e.g., OECD, others): None provided.

GLP: YES [ ]
NO [X]

Test Results: Autoignition temperature = 371°C

Cool flame autoignition = 199°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

3.8 **pH in Water**

pH at mg/L (Water)

pKa = 4.8 at 25°C

Method (e.g., OECD, others): Not provided.

GLP: YES [ ]
NO [X]

Comments: Data predates GLP regulations.

Reference: Product literature, Union Carbide Corp. (1974).

3.9 **Other Data**

Density: 0.90 cc at 20°C

Comments: Study predates GLP regulations.

Reference: Material Safety Data Sheet, Eastman Kodak Company.

4.0 **Source of Exposure**

* 4.1 **Production Levels Expressed as Tonnes Per Annum:** 5,000 - 50,000 tonnes per year (TSCA inventory of 1977 production levels).

4.2 **Processes:** 2-Ethylhexanoic acid is manufactured by the air oxidation of 2-ethylhexaldehyde, using a continuous enclosed computer-controlled process. The crude product is purified by extractive removal of water-soluble impurities and by distillation. The product is transferred through closed, dedicated lines to storage tanks.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

* 4.3 **Information Concerning Uses** (including categories and types of uses expressed in percentage terms): The primary use for 2-ethylhexanoic acid is as an industrial intermediate for chemical conversion to metallic salts, which are used as paint dryers. The substance may also be used as an industrial intermediate in the manufacture of catalysts, plasticizers, inks and dyestuffs, drugs, flame retardants, surfactants and lubricants. 2-Ethylhexanoic acid is not sold as a consumer formulation in the United States.

4.4 **Options for Disposal:** Non-aqueous wastes are incinerated and aqueous wastes are sent to a waste-water treatment facility for biodegradation.

4.5 **Other Remarks:**

Information Concerning Human Exposure: Approximately 400 people may be exposed to 2 ethylhexanoic acid during manufacture and use in the United States. Because 2-ethylhexanoic acid has a low volatility, the potential for atmospheric release or inhalation exposure is minimal. Dermal exposure is minimized by the enclosed, automatic nature of the manufacturing process, and bulk handling and transfer. The potential dermal exposure is further minimized by requiring all workers to wear dermal protection, such as impermeable gloves, when taking four-ounce quality control samples (which is an approximately 2-minute operation, conducted by one worker about eight times daily).

Shipment of 2-ethylhexanoic acid to customers is primarily by tank car or tank truck. A small percentage (approximately 3%) is shipped in drums. Customers typically receive the material through closed lines, and store in tanks prior to use. The substance is subsequently transferred to enclosed reactors for chemical conversion to other substances. Beyond this point, there is no exposure to 2-ethylhexanoic acid, as it ceases to exist as a chemical.

Reference: Roderick D. Gerwe, Ph.D., Eastman Chemical Company

5.0 Environmental Fate and Pathways

* 5.1 **Degradability (Biotic and Abiotic)**

5.1.1 **Biodegradability**

Test Substance: 2-Ethylhexanoic acid

Test Type: aerobic [X], anaerobic [ ]

Test Medium: Activated, non-acclimated sludge

In the case of poorly soluble chemicals, treatment given (nature, concentration, etc.):

Test Method: According to Price, K.S., Waggy, G.T., and Conway, R.A. (Brine Shrimp Bioassay and Seawater BOD of Petrochemicals, J. Water Poll. Control Fed. 46, 63-77, 1974). Similar to OECD Guideline 301D. Concentrations of 3, 7, and 10 mg/L used. BOD determined after 5, 10, and 20 days.

GLP: YES [ ]
NO [X]

Test Results: BOD_5 = 60 % of Theoretical (2.44 g O_2/g test substance).
BOD_{10} = 76 % of Theoretical (2.44 g O_2/g test substance).
BOD_{20} = 83 % of Theoretical (2.44 g O_2/g test substance).

Comments: Study predates GLP regulations.

Reference: G.T. Waggy. 1994. Union Carbide Chemicals and Plastics Company, Inc., South Charleston, WV.

5.1.2 **Sewage Treatment**

Comments: No Data Available.

5.1.3 **Stability in Air** (e.g., photodegradability)

Test Substance:

Test Method or Estimation Method (e.g., OECD, others): Calculation

GLP: YES [ ]

NO [X]

Test Results: 2-Ethylhexanoic acid is not expected to enter the air as a vapor due to its low vapor pressure.

Reference: Staples, 2000.

5.1.4 **Stability in Water** (e.g., hydrolysis):

Test Substance:

Test Method: Calculation

GLP: YES [ ]
NO [X]

Test Results: See Staples report.

Reference: Staples, 2000.

5.1.5 **Identification of Main Mode of Degradability in Actual Use**

No Data Available.

5.2 **Bioaccumulation**

Test Substance:

Test Method (e.g., OECD, others): Calculated

GLP: YES [ ]
NO [X]

Test Results: see Staples report

Bioaccumulation Factor:

Calculated Results:

Comments:

Reference: Staples, 2000.

* 5.3 **Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathways**

Because of its low vapor pressure (see Section 3.3), 2-Ethylhexanoic acid is not expected to be transported to the air. Transport to soil is possible where biodegradation is expected since 2-Ethylhexanoic acid is readily biodegradable (see Section 5.1).

Type of Transport and Distribution Processes between Compartments (e.g., air, water, soil):

Distribution to water is not expected because 2-Ethylhexanoic acid has a low water solubility (see Section 3.5).

Estimation of Environmental Concentrations:

Reference: Staples, 2000.

5.4 **Monitoring Data** (Environment):

No Data Available.

6.0 **<u>Ecotoxicological Data</u>**

* 6.1 **Toxicity to Fish**

6.1.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Pimephales promelas (fathead minnow)

Test Method: Test method 231, Toxicity to Fish, in Standard Methods for the Examination of Water and Wastewater (1971). Ten adult minnows per concentration were exposed for 96 hours.

· Type of test static [X], semi-static [ ], flow-through [ ]
Other (e.g., field observation) [ ]

GLP: YES [ ]
NO [X]

Test Results: LC_{50} = 70 mg/L after 96 hours at a pH of 5.3-5.5

Comments: Study predates GLP regulations. Test solutions were not buffered.

Reference: Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

6.1.2 **Results of Long-Term Tests** e.g., prolonged toxicity, early life stage

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.2 **Toxicity to Daphnids**

6.2.1 **Results of Acute Tests**

Test Substance: 2-Ethylhexanoic acid

Test Species: Daphnia magna (waterflea)

Test Method (e.g., OECD, others): Daphnid Acute Toxicity Test - "Guideline For Testing Chemicals", EG-1, EPA, Office of Toxic Substances, Jan. 1982, 75-009 (1975).

Test Concentration: 31.25, 62.5, 125, 250, & 500 mg/L.

Test Duration: 48 hours.

GLP: YES [ ]
NO [X]

Test Results: 48 hr EC_{50} = 85.38 mg/L (slightly toxic),
CI 95% = 79.77-91.38 mg/L
48 hr EC_0 = 62.5 mg/L, 48 hr EC_{100} = 125 mg/L

Comments: No analytical measurements available. Tested at nominal concentrations ranging from 31.25-500 mg/L. (EC_0 - highest tested concentration without effect after 48 hours. EC_{100} - lowest tested concentration with 100% effect after 48 hours).

Reference: BASF Aktiengessellschaft Report # 1/0949/2/88 - 0949/88 dtd. 04-11-1988. Entitled "Determination of the Acute Toxicity of 2-Ethylhexansaeure to the Waterflea *Daphnia magna straus*."

6.2.2 **Results of Long-Term Tests e.g., Reproduction**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.3 **Toxicity to Algae**

Test Substance: 2-Ethylhexanoic acid

Test Species: Scenedismus subspicatus

Test Method (e.g., OECD, others): Inhibition of Algal Replication Following DIN 38412 L9.

Test Concentration: 0, 25, 50, 100, 250, or 500 mg/L.

Test Duration: 96 hours.

GLP: YES [ ]
NO [X]

Test Results: 72 hr EbC_{10} = 32.543 mg/L
72 hr EbC_{50} = 60.511 mg/L

96 hr EbC_{10} = 24.496 mg/L
96 hr EbC_{50} = 40.616 mg/L

72 hr EuC_{10} = 31.940 mg/L
72 hr EuC_{50} = 49.279 mg/L

96 hr EuC_{10} = 27.938 mg/L
96 hr EuC_{50} = 44.390 mg/L

Comments: Nominal concentrations tested. No analytical available on test concentrations.

Reference: BASF AG. Report # BASF 2/0949/88, dated 10/24/1989.

6.4 **Toxicity to Other Aquatic Organisms**

Test Substance:

Test Species:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

6.5 **Toxicity to Bacteria**

Test Substance:

Test Species:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 6.6 **Toxicity to Terrestrial Organisms**

6.6.1 **Toxicity to Soil Dwelling Organisms**

Test Results: No Data Available.

6.6.2 **Toxicity to Plants**

Test Results: No Data Available.

6.6.3 **Toxicity to Birds**

Test Results: No Data Available.

6.7 **Biological Effects Monitoring (Including Biomagnification)**

Test Results: No Data Available.

6.8 **Biotransformation and Kinetics in Environmental Species**

No Data Available.

7.0 **Toxicological Data** (oral, dermal and inhalation, as appropriate)

* 7.1 **Acute Toxicity**

7.1.1 (A.) **Acute Oral Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Male Wistar Rats

Test Method: Groups of 6 rats were treated by gavage with 2-ethylhexanoic acid in water. Animals were observed for mortality over the course of fourteen days.

GLP: YES [ ]
NO [X]

Test Results: Discriminating dose (for fixed dose only): LD_{50} = 3000 g/kg

Comments: Study predates GLP regulations. Body weights not measured; clinical signs of toxicity not described. No information provided on dosing solution.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Oral Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rats/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Two animals (sex not specified) per group were treated with either 100, 200, 400, 800, 1600, or 3200 mg/kg by gavage and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: Transient signs of weakness and ataxia immediately after dosing were described. There was no effect on body weight.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments: Study predates GLP regulations. Test sample not analyzed. Onset and duration of clinical signs of toxicity not indicated. Body weight data not provided. Preparation of dosing solution not indicated. No indication of fasting.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(C.) **Acute Oral Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.6%) in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method: Eastman Kodak Company, Health and Environment Laboratories Protocol. Non-fasted animals (4 per group) were treated with either 0, 100, 800, 1600, or 3200 mg/kg in a single dose by gavage and observed for 14 days.

GLP: YES [X]
NO [ ]

Test Results: Animals treated with 800, 1600, and 3200 mg/kg appeared slightly to severely weak immediately after dosing. Animals given 3200 mg/kg were prostrate 4 hours after treatment. Animals in the other groups were normal immediately after dosing. By 24 hours post-treatment, animals treated with 3200 mg/kg died, but all other animals appeared normal. All surviving animals gained weight. No gross pathology was observed in any surviving animal, and animals that died on test had no distinctive gross pathology.

LD50 or other measure of acute toxicity (e.g. in case of fixed-dose test): 1600-3200 mg/kg

Comments:

Reference: Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Health and Environment Laboratories, Eastman Kodak Company.

7.1.2 **Acute Inhalation Toxicity**

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rat/strain not specified

Test Method: Eastman Kodak Company, Laboratory of Industrial Medicine Protocol. Three rats (sex not specified) exposed to nominal concentration of 2.36 mg/L (400 ppm) for 6 hours and observed for 14 days.

GLP: YES [ ]
NO [X]

Test Results: No mortality or clinical signs of toxicity occurred. Animals gained weight.

LC50: NA

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.1.3 Acute Dermal Toxicity

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: Guinea pig/strain not specified

Test Method: Six animals (sex not specified) were treated with the test material in an occluded patch for four days and observed for a total of 14 days.

GLP: YES [ ]
NO [X]

Test Results: LD50: 6.5 ml/kg

Comments: Study predates GLP regulations. No clinical observations cited. Body weights not measured.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

(B.) **Acute Dermal Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for mortality. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Both animals receiving neat (undiluted) 2-ethylhexanoic acid died. No mortality occurred with the 20% preparation, but the animal receiving 20 ml/kg of the 20% preparation lost weight.

LD50: < 5.0 ml/kg

Comments: Study predates GLP regulations. Body weight data not provided.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

7.2 Corrosiveness/Irritation

7.2.1 Skin Irritation

(A.) **Test Substance**: 2-Ethylhexanoic acid (undiluted, 20% in 90% acetone/10% corn oil)

Test Species/Strain: Guinea pig/strain not specified

Test Method: Two animals (sex not specified) were treated with the either 5 or 10 ml/kg of undiluted test material in an occluded patch for 24 hours and observed for irritation. Three additional animals received 5, 10, or 20 ml/kg of 20% 2-ethylhexanoic acid in 90/10 acetone/corn oil by occluded patch.

GLP: YES [ ]
NO [X]

Test Results: Slight edema, erythema, and necrosis was observed with neat material. No edema or very slight edema, with slight to moderate redness, was observed after treatment with the 20% solution.

Comments: Study predates GLP regulations.

Reference: Fassett, D.W. (1955). Toxicity Report (Unpublished report). Laboratory of Industrial Medicine, Eastman Kodak Company.

(B.) **Skin Irritation** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: New Zealand White Rabbit

Test Method: US Department of Transportation Corrosivity Test

GLP: YES [X]
NO [ ]

Test Results: The test material produced slight necrosis in 5 of 6 animals after 4 hours with subsequent eschar formation (slight to moderate).

Comments:

Reference: Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Health and Environment Laboratories, Eastman Kodak Company.

7.2.2 Eye Irritation

Test Substance: 2-Ethylhexanoic acid

Test Species/Strain: Rabbit/strain not designated

Test Method (e.g., OECD, others): Volumes of 0.001, 0.005, 0.02, 0.1, or 0.5 mL were instilled into the eye of albino rabbits and the eyes evaluated after 24 hours using fluorescein stain.

GLP: YES [ ]

NO [X]

Test Results: Severe corneal irritation was observed

Comments: Study predates GLP regulations. No indication of the number of animals used. No indication of the extent of irritation or corneal opacity. No observation beyond 24 hours to indicate recovery.

Reference: Smyth, Jr., H.F., and Carpenter, C.P. (1944). The Place of the Range Finding Test in the Industrial Toxicology Laboratory, J. Ind. Hyg. Toxicol. 26, 269-273.

7.3 Skin Sensitisation

Test Substance:

Test Method:

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.4 **Repeated Dose Toxicity**

(A.) **Test Substance:** 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides. The liver was analyzed biochemically for peroxisome activity and evaluated microscopically for the presence of peroxisomes.

GLP: YES [ ]
NO [X]

Test Results: Animals fed the diet containing 2-ethylhexanoic acid gained 15% less weight than did control animals. Relative (to body weight) liver weight was 55% higher in treated animals compared with control animals. Liver catalase and carnitine acetyltransferase activities were significantly increased in treated animals. The ratio of mitochondria to peroxisomes was approximately 1:1 compared with the control animals which had a ratio of 5:1, indicating a substantial increase in peroxisome proliferation. Cholesterol and triglyceride levels were significantly decreased.

Comments: No indication of absolute liver weight given. No data of triglyceride and cholesterol levels provided. Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1978). Hepatic Peroxisome (Microbody) Proliferation in Rats Fed Plasticizers and Related Compounds. Toxicol. Appl. Pharmacol. 45, 497-504.

(B.) **Repeated Dose Toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Male Fischer 344 Rats

Test Method: Animals were fed a diet containing either 0 or 2% 2-ethylhexanoic acid for 3 weeks after which blood was analyzed for cholesterol and triglycerides.

GLP: YES [ ]
NO [X]

Test Results: Cholesterol levels in treated animals were 17% below the level in control animals, and triglycerides were 68% less than in controls.

Comments: Study predates GLP regulations.

Reference: Moody, D.E., and Reddy, J.K. (1982). Serum Triglyceride and Cholesterol Contents in Male Rats Receiving Diets Containing Plasticizers and Analogues of the Ester 2-Ethylhexanol. Toxicol. Lett. 10, 379-383.

(C.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: B6C3F1 Mice

Test method: Male and female mice (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: One animal from the mid-dose group was found dead and one control animal was euthanatized in extremis. Gait disturbance and weakness were observed in one high-dose female during the first two days of treatment. All other animals appeared normal except for the control animal that was euthanatized. Body weights and feed consumption were unaffected by treatment. High-dose male mice had increased absolute and relative (to body weight) liver weight which was associated with hypertrophy of the hepatocytes. Liver weight and microscopic morphology of all other groups were comparable to controls. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 800 mg/kg for males and 1600 mg/kg for females.

Comments:

Reference: Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Health and Environment Laboratories, Eastman Kodak Company.

(D.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (>99.8%) in corn oil

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 200, 800, or 1600 mg/kg by gavage 5 days per week for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed

consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Five animals (three male and two female) in the high-dose group were found dead, and three additional animals from this group were euthanatized in extremis. No mortality occurred in other groups. Weakness and lethargy, hypothermia, sialorrhea, tremors, and poor body condition were observed high-dose animals. Mid-dose animals showed weakness, lethargy, and sialorrhea, generally less severe than in the high-dose animals. All other animals appeared normal. Body weights in surviving high-dose animals were 10-20% less than in the control group. Mid-dose male rats also had significantly lower body weight compared with the control group, but mean body weight in mid-dose females and low-dose groups was comparable to the control group. Feed consumption in surviving high-dose animals was decreased, while in all other groups was comparable to controls. High- and mid-dose rats had dose-related increased absolute and relative (to body weight) liver weight. High-dose animals which survived to termination had hepatocyte hypertrophy. Animals that died on test had minimal hepatocyte degeneration. Microscopic morphology of the liver of all other groups were normal. No treatment-related changes were observed in the kidneys. The no-observable-effect level (NOEL) was 200 mg/kg for males and < 200 mg/kg for females.

Comments:

Reference: Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Health and Environment Laboratories, Eastman Kodak Company.

(E.) **Repeated dose toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: Male and female mice (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]

NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 1608-1965, 3084-3986, and 5794-9229 mg/kg/day for the low-, mid, and high-dose groups, respectively. One male from the mid-dose group was found dead during the study. The cause of death was not apparent. All other animals appeared normal. Animals fed 3.0% 2-ethylhexanoic acid lost weight during the first few days, and did not gain weight during the remainder of the study. Males fed the 1.5% diet had lower body weights on Day 14 compared to the control group. Body weights in the other groups were comparable to the control group. Feed consumption was initially reduced in treated groups, but was comparable to the control group thereafter. Absolute and relative (to body weight) liver weight of animals in the high- and mid-dose groups (male and female) were significantly higher than in the control groups. Hepatocyte hypertrophy, primarily in the portal region, was observed in all groups except a few low-dose animals. The severity decreased with dose from moderate in the high-dose groups, to minor in the mid-dose groups, to minimal in the low-dose groups. Coagulative necrosis of the hepatocytes was also observed in treated male groups and in the high-dose female group. The severity was described as minimal and the lesion multifocal. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Health and Environment Laboratories, Eastman Kodak Company.

(F.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer-344 Rats

Test Method: Male and female rats (5 per sex per group) were treated with 0, 0.75, 1.5, and 3.0% 2-ethylhexanoic acid in feed for 2 weeks. Animals were observed each workday for clinical signs of toxicity. Body weights and feed consumption were measured twice weekly. At termination, the liver of each animal was weighed, and the liver and kidneys examined microscopically.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, the doses received were 706-756, 1351-1411, and 2276-2658 mg/kg/day for the low-, mid, and high-dose groups, respectively. High-dose animals had slightly reduced amounts of feces on Days 2 and 3, and periodically they appeared unkempt, but no other signs of toxicity were observed. High-dose animals lost weight initially, and had low weight gains during the remainder of the study. Mid-dose male rats also had a reduced weight gain during the study, and had significantly lower body weights

only at termination compared with the control group. All other groups gained comparable amounts of weight. Feed consumption was reduced in the high- and mid-dose groups. Absolute and relative (to body weight) liver weight were significantly increased in a dose-related manner. Hepatocyte hypertrophy and coagulative necrosis were observed in high- and mid-dose animals. The severity and/or incidence of these lesions were lower in the mid-dose group compared with the high-dose group. No changes in the kidneys were described. A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%.

Reference: Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Health and Environment Laboratories, Eastman Kodak Company.

(G.) **Repeated Dose Toxicity** (Additional study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: B6C3F1 Mice

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 180-205, 885-1038, and 2728-3139 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose group compared with the control group. Body weights in the high-dose groups were significantly lower than in the control group beginning after the first week, and body weights in mid-dose females were significantly lower than in controls only after 13 weeks. Male mid- and all low-dose groups were unaffected by treatment. No changes in hematology occurred. Cholesterol levels were significantly higher in mid-dose and high-dose mice, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. Bilirubin was significantly lower in the high-dose groups, and in the mid-dose female group, compared with the control group. Incidental changes in urea nitrogen and alanine transaminase were not considered to be treatment-related. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose groups compared with the control groups. Relative (to brain weight) liver weight of male and female mice fed 0.5%, and absolute and relative (to body weight) liver weight of male mice fed 0.5% were significantly

higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose groups after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. High-dose mice also had cytoplasmic basophilia of the proximal convoluted tubules, and male high-dose mice had acanthosis and hyperkeratosis of the non-glandular forestomach. All toxicity was reversible within 28 days. The no-observable-adverse-effect level (NOAEL) was 0.1% 2-ethylhexanoic acid in the diet (approximately 200 mg/kg/day). A NOEL was not determined.

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Health and Environment Laboratories, Eastman Kodak Company.

(H.) **Repeated Dose Toxicity** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid (99.9%) in feed

Test Species/Strain: Fischer 344 Rats

Test Method: USEPA TSCA Health Effects Testing Guideline (CFR 40 798.2650) with satellite groups. Similar to OECD Guideline 408. Animals fed diets containing 0, 0.1, 0.5, and 1.5% 2-ethylhexanoic acid for 13 weeks with satellite groups allowed 28 days of recovery.

GLP: YES [X]
NO [ ]

Test Results: Based on feed consumption and body weight, doses received were 61-71, 303-360, and 917-1068 mg/kg/day for the low-, mid, and high-dose groups, respectively. No mortality or treatment-related signs of toxicity occurred. Body weight gain and feed consumption were slightly lower in the high-dose groups compared with the control group. Body weights were significantly lower than in the control group beginning after the first week. Mid- and low-dose groups were unaffected. Minor changes in hematology occurred (lower mean corpuscular hemoglobin and mean corpuscular volume) in mid-dose male, and high-dose males and females. Cholesterol levels were significantly higher in treated male rats, but triglyceride levels were significantly lower in mid-dose female, and high-dose male and female groups, compared with the control group. BUN and albumin were significantly higher in high-dose males. Absolute and relative (to body and brain weight) liver weights were significantly higher in the high-dose group compared with the control group. Absolute and relative (to brain weight) liver weight of

female rats fed the 0.5% diet, and relative (to body weight) liver weight of male and female rats fed the 0.5% diet were significantly higher compared with the control group. Minor increases in relative organ weights occurred for other organs (kidney, adrenals, brain, testes), but were considered to reflected lower terminal body weight. Hepatocyte hypertrophy and eosinophilia were observed in the liver of mid- and high-dose animals after 13 weeks of treatment. The severity and incidence was lower in the mid-dose group compared with the high-dose group. All toxicity was reversible within 28 days. The NOAEL was 0.5% 2-ethylhexanoic acid in the diet (approximately 300 mg/kg/day). The NOEL was 0.1% 2-ethylhexanoic acid in the diet (approximately 65 mg/kg/day).

Comments: 2-Ethylhexanoic acid mixed with corn oil prior to mixing in feed. Total concentration of corn oil was 2%. Additional corn oil may have contributed to the increase in cholesterol.

Reference: Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Health and Environment Laboratories, Eastman Kodak Company.

* 7.5 **Genetic Toxicity**

7.5.1 **Bacterial test**

(A.) **Test Substance:** 2-Ethylhexanoic acid

Test Species/Strain: S. typhimurium TA98 and TA100, with and without S-9

Test Method: Incubation with test substance for 2 days at 37°C in standard Ames test.

GLP: YES [ ]

NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation:	2.9 mg/plate
without metabolic activation:	2.9 mg/plate

Concentration of the test compound resulting in precipitation: Not determined

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]

without metabolic activation: [ ] [ ] [X]

Comments: No control values provided.

Reference: Warren, J.R., Lalwani, N.D., and Reddy, J.K. (1982). Phthalate Esters as Peroxisome Proliferator Carcinogens. Environ. Health Perspec. 45, 35-40.

(B.) **Bacterial Test** (Preferred Study)

Test Substance: 2-Ethylhexanoic acid in DMSO

Test Species/Strain: Salmonella typhimurium/TA-97, TA-98, TA-100, and TA-1535.

Test Method: Modified from Haworth et al., 1983. Environ. Mutagen 5 (Suppl 1):3-142. Concentrations of S-9 from rats or hamsters treated with Aroclor 1254 varied between 10 and 30%.

GLP: YES [ ]
NO [X]

Test Results: Minimum concentration of test substance at which toxicity to bacteria was observed:

with metabolic activation: 3.3 mg/plate
without metabolic activation: 3.3 mg/plate

Concentration of the test compound resulting in precipitation:

Genotoxic effects:

	+	?	-
with metabolic activation:	[ ]	[ ]	[X]
without metabolic activation:	[ ]	[ ]	[X]

Comments: Conducted as part of Government contract. Not under GLP regulations.

Reference: Zeiger, E., et al., (1988). Salmonella Mutagenicity Test: IV. Results From the Testing of 300 Chemicals, Environ. Mol. Mutagen. 11, 1-158.

7.5.2 **Non-Bacterial *In Vitro* Test**

Test Substance:

Test Method (e.g., OECD, others):

GLP: YES [ ]

NO [ ]

Test Results: No Data Available.

Comments:

Reference:

7.5.3 **Non-Bacterial Test *In Vivo***

Test Substance: 2-Ethylhexanol in corn oil (see comments)

Test Species/Strain: Mouse/B6C3F1

Test Method (e.g., OECD, others): Micronucleus test - Six male and six female mice were injected intraperitoneally with either a once or twice within 24 hours with 456 mg/kg. Control groups (same numbers/sex) recieved corn oil only. A positive control group received triethylene melamine. Micronuclei were determined in the polychromatic erythrocytes.

GLP: YES [X]
NO [ ]

Test Results: There were no increased incidences of micronuclei in polychromatic erythrocytes in the female groups receiving 2-EH. The male group that received a single intraperitoneal injection of 456 mg/kg 2-EH did not have an increased incidences of micronuclei in polychromatic erythrocytes. An increased incidence of micronuclei in the male group that received two intraperitoneal injections of 456 mg/kg 2-EH was attributed to an unusually low incidence of micronuclei in the cotnrol group. The values for all the treated groups (up to 0.28%) was within the normal range for the testing laboratory.

Comments: 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. (Other studies with 2-ethylhexanol are available and listed in the SIDS Dossier for that chemical; however, this study seemed the most relevant).

Reference: Litton Bionetics Inc., (1982) Mutagenicity Evaluation of 2-ethylhexanol (2-EH) in the mouse micronucleus test. See also CMA Communication from the Chemical Manufacturers Association to the Employment Accident Insurance Fund of the Chemical Industry. (1982). (See also EPA OTS508477)

7.6 **Carcinogenicity**

Test Substance:

Test Species/Strain:

Test Method (e.g., OECD, others):

GLP: YES [ ]
NO [ ]

Test Results: No Data Available.

Comments:

Reference:

* 7.7 **Reproductive and Developmental Toxicity**

7.7.1 **Reproductive Toxicity**

Test Substance: Sodium 2-Ethylhexanoate (99.5%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): According to OECD Guideline 415, One-Generation Reproduction Toxicity Study. Male and female rats were treated with 0, 100, 300, or 600 mg/kg of test substance in the drinking water prior to mating (10 weeks for males and two weeks for females) and during cohabitation. Pregnant females were treated during gestation and lactation. Body weights and feed consumption were measured weekly. Water consumption was measured, but the interval was not stated. The concentration of the test substance in the drinking water was adjusted for changes in body weight in order to provide the appropriate dose level.

GLP: YES [ ]
NO [X]

Test Results: The test substance did not produce mortality or clinical signs of toxicity in males. Body weights, feed consumption, and overall water consumption were unaffected. The relative epididymidal weights in high-dose males were significantly increased, but no histologic changes occurred in this tissue or in the testes. Slight decreases in sperm count (14%) were noted in high-dose males, but these were not statistically significant. Alterations in sperm motility were not treatment-related, and there was no effect on fertility. An apparent, but not statistically significant, slight increase in the number of abnormal sperm was noted in the highest two dose groups; however, the incidence per animal was not provided. The high-dose of 600 mg/kg significantly reduced overall water consumption in pregnant females. Body weights of high-dose females were

slightly reduced prior to mating (5%), and this difference was exaggerated during pregnancy to the point that significant differences were noted on Days 7, 14, and 21. However, the weekly relative weight gains were comparable among groups. No differences in body weight were noted at any other time. No effects on fertility were indicated, although the authors note that treated groups required more time to successfully complete mating. The mean litter size in high-dose pregnant females was significantly reduced (decreased by one pup). Individual animal data were not provided to determine if this reflected all dams or only selected dams. A significant increase in "kinky tail" was observed in the pups from mid- and high-dose females (~25%), but the response was not dose-related. This variation was also observed in the control group (~5%). The mean pup weights in the high-dose group were significantly lower on postnatal day 7 and 14 compared with the control group. Physical development of the eyes, teeth, and hair appeared to be slightly later in the pups from the high-dose groups compared with the control group. The differences noted were typically one or two days, but the significance of this finding is unclear since no data were presented on the length of gestation in treated and control dams. Reflex responses were not affected.

NOEL for P generation: 300 mg/kg

NOEL for F1 generation: 100 mg/kg

Comments: Water consumption was measured, but the interval was not stated. Water consumption values were not provided to ascertain the extent of unpalatability. The concentration of the test substance in the drinking water was not provided, and there was no analysis of dosing solutions. The incidence of an effect within an animal (such as for sperm morphology) or litter (such as for kinky tail) was not provided. Such information would be helpful to evaluate if the effects are nested in single individuals or litters.

Also, no criteria were provided to indicate how many abnormal sperm were necessary to be considered a positive response. This involved only a few animals, and whether the effect involved specific males or females was not identified. Since all animals were naive and not proven breeders, reduced mating success may not be treatment related. It is also not known how much the unpalatability of treated drinking water stressed the animals. No confirmation of estrous cycle was performed. No data on the effect of the test substance on gestation period were presented. Thus, the apparent effect on physical development of pups from the high-dose group dams may be the result of early delivery which could present the appearance of a slight delay in development. The variability of the data for sperm numbers and motility was as high as 50% and was not considered to be reproducible between animals in a group to be a reliable indicator of male function.

Histopathology of reproductive organs in the Repeated Dose Studies in Sprague-Dawley rats did not indicate any morphologic changes even after 13 weeks of dietary treatment with doses of approximately 1000 mg/kg/day. Developmental toxicity studies in Fischer-344 rats or NZW rabbits have not indicated any early

fetal mortality or effects on viable or non-viable litter size. Wistar rats have demonstrated a susceptibility to the developmental effects of this test substance.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., Kosma, V.-M., and Komulainen, H. (1993). Effects of 2-Ethylhexanoic acid on Reproduction and Postnatal Development in Wistar Rats. Fundam. Appl. Toxicol. in press.

7.7.2 (A.) **Teratogenicity/Developmental Toxicity**

Test Substance: 2-Ethylhexanoic acid (neat)

Test Species/Strain: Wistar Rats

Test Method (e.g., OECD, others): Seven to ten pregnant females per group were treated by gavage with a single dose of either 0, 1.0, or 2.0 ml/kg 2-ethylhexanoic acid (approximately 900 or 1800 mg/kg) on Day 12 of gestation and dams euthanatized on Day 20. Fetuses were preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [ ]
NO [X]

Test Results: The high dose produced embryo- and fetal-toxicity based on the 30% decrease in fetal weight, and 30% increased in percentage dead and resorbed fetuses (from 9.6 in controls to 12.9 in the high-dose). The percentage of malformed fetuses increased from 0 in control animals to 67.8% in the high dose dams. No apparent toxic or teratogenic effect was observed at the low dose. Defects observed included hydronephrosis, levocardia, septal defects, short and kinky tail, ectrodactyly, misplaced digits, and bowed radius.

The percentages of surviving fetuses with anomalies are: 20.9% hydronephrosis; 10.1% cardiovascular; 15.5% tail (skeletal); 51.2% limb (skeletal); and 10.9% other (not specified).

NOEL for maternal animals = Not determined

NOEL for offspring = 0.9 g/kg

Comments: Maternal effects were not described. There was no indication of effects on sex of fetuses. The number of animals per group is low (only 7), and fetal data are presented as percentages of affected fetuses per litter. Thus, one or two litters could have adversely affected the data. No data of anomalies in control animals were presented. There was no analysis of dosing solutions.

Reference: Ritter, E.J., Scott, Jr., E.J., Randall, J.L., and Ritter, J.M. (1987). Teratogenicity of Di(2-ethylhexyl) Phthalate, 2-Ethyhexanol, 2-Ethylhexanoic Acid, and Valproic Acid, and Potentiation by Caffeine. Teratol. 35: 41-46.

(B.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: Han:NMRI Mice

Test Method (e.g., OECD, others): Nine to 20 pregnant female mice were injected ip with a total dose of 500 or 2000 mg/kg/day (4 x 500 mg/kg per day) of sodium 2-ethylhexanoate (racemic mixture and R- and S-enantiomers) on Day 8 of gestation. Dams were sacrificed on Day 18 and examined for the number of implantations, live and dead fetuses, and early resorptions. Live fetuses were weighed and examined for exencephaly.

GLP: YES [ ]
NO [X]

Test Results: A dose of 2000 mg/kg/day of the (R) enantiomer or racemic mixture produced ~10% embryolethality and 16% lower fetal weight. Of the total fetuses examined in these groups, 32 and 59% had exencephaly (racemic mixture and (R) enantiomer, respectively). There is no indication of the number of litters affected. The same dose of the (S) enantiomer and 500 mg/kg/day of the racemic mixture were not fetotoxic or teratogenic since embryolethality and fetal weight were at control levels.

NOEL for maternal animals = Not determined

NOEL for offspring = 500 mg/kg/day for the racemic mixture, 2000 mg/kg/day for the (S) enantiomer. Not determined for the (R) enantiomer.

Comments: Author states that Han strain of mouse used demonstrates susceptibility to exencephaly. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed four times per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs of toxicity) were provided. There was no analysis of the dosing solutions.

Reference: Hauck, R.-S., Wegner, C., Blumtritt, P., Fuhrhop, J.-H., and Nau, H. (1990). Asymmetric Synthesis and Teratogenic Activity of (R)- and (S)-2-Ethylhexanoic Acid, A Metabolite of the Plasticizer Di-(2-ethylhexyl)phthalate. Life Sci. 46, 513-518.

(C.) **Teratogenicity/Developmental Toxicity** (Additional Study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in drinking water

Test Species/Strain: Wistar rats

Test Method (e.g., OECD, others): Similar to Guideline 414. Mated female rats were treated from Gestation Days 6-19 with either 0, 100, 300, or 600 mg/kg/day of the test substance in drinking water. Clinical signs of toxicity were observed daily. Body weight was measured weekly. Feed consumption was measured during Gestation Days 13-16. Water consumption was measured during the treatment period, but the frequency was not stated. Dosing solutions were adjusted periodically to maintain the appropriate dose based on changes in body weight. All animals were sacrificed on Day 20 and examined for live and dead fetuses, resorptions, corpora lutea, implantation sites, and pup weights. Half the fetuses were examined for visceral anomalies, while the other half were stained for skeletal examination.

GLP: YES [ ]
NO [X]

Test Results: The pregnancy rate (successful matings) was slightly lower in the mid- and high-dose groups, but the difference was not statistically significant. There were no clinical signs of toxicity. Body weights of high-dose females were reduced 10% on Day 13, and were significantly lower (11%) on Day 20 compared with the control group. Corrected maternal body weights at termination and weight gains of high-dose females were significantly lower than for the control group. The weight of the gravid uterus was not significantly different, however.

Water consumption was also significantly reduced (up to 20% less than controls), but no data were presented. No differences in feed consumption were noted. No gross pathologic changes were noted in dams.

Mean fetal weight per litter was significantly reduced in the mid- and high-dose groups. Mean placental weights were also significantly reduced. There were no effects on the number of live fetuses or resorptions (early or late). No visceral abnormalities were noted. Clubfoot was the only skeletal malformation noted in mid- and high-dose groups, both having significantly higher percentages of affected fetuses per litter (5-6% versus 0%) than in the control group. Some changes in skeletal variations were noted. The percentages of fetuses per litter with wavy ribs were significantly higher in all treated groups compared with the control group, and the percentages of fetuses per litter with reduced cranial ossification were also significantly higher in the low- and high-dose groups compared with the control group. The percentage of fetuses with twisted hind legs was significantly higher in

the mid-dose group (7%) compared with the control group (1%). The number of litters affected were not indicated.

NOEL for maternal animals = 300 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Comments: There is no indication that changes in water consumption were taken into account when adjusting the concentration of the dosing solution. Also, the frequency of water consumption measurement and adjustments in .the concentration of the dosing solution were not indicated. The number of litters affected were not indicated. As a result, litter effects could not be evaluated.

Reference: Pennanen, S., Tuovinen, K., Huuskonen, H., and Komulainen, H. (1992). The Developmental Toxicity of 2-Ethylhexanoic Acid in Wistar Rats. Fundam. Appl. Toxicol. 19:505-511.

(D.) **Teratogenicity/Developmental Toxicity** (Additional study)

Test Substance: Sodium 2-Ethylhexanoate (99%) in physiological saline

Test Species/Strain: SWV and C57BL/6NCrlBR Mice

Test Method (e.g., OECD, others): Three to 22 pregnant female mice were injected with multiple doses per day of 403 to 1037 mg/kg of sodium 2-ethylhexanoate. The results of four separate experiments are reported: one to evaluate maternal toxicity following a single subcutaneous injection on Gestation Day 8.0 with 807-1037 mg/kg/day of a racemic mixture of test substance; one to compare the response of SWV and C57 mice injected intraperitoneally on Days 7.5, to 9.0 with 1152 mg/kg/day (2 x 576 mg/kg per day) of a racemic mixture; one comparing the fetotoxicity in animals injected intraperitoneally on Gestation Days 7.0-10.0 with total dose of 1728 mg/kg given as three injections of 576 mg/kg of a racemic mixture over a 36 hour preiod; and one comparing the fetotoxicity of a total dose of 1209-2592 mg/kg (given as 3 injections of 403-864 mg/kg over 36 hour period) the (S) and (R) enantiomers injected ip on Days 8.0-9.0.

GLP: YES [ ]
NO [X]

Test Results: Three dams injected sc on Gestation Day 8 with 807 mg/kg of a racemic mixture of sodium 2-ethylhexanoate survived to Day 18, but mortality occurred at 864 and 1037 mg/kg/day (1/7 and 5/6, respectively). Three additional dams injected on Day 8.5 with 864 mg/kg also survived to Day 18. The authors also provide data on the number of resorptions versus implantation sites in these animals. These data indicate that the percentage of resorptions increased at higher dose levels, and was also high in the

animal that survived the 864 mg/kg dose on Day 8.5. However, no control data were provided for comparison.

A comparison of the susceptibility of the SWV and C57 strains indicated that after 4 consecutive injections with 1152 mg/kg/day (racemic mixture) on Days 7.5, 8.0, 8.5, and 9.0, the SWV strain had 49% exencephaly (51/104 live fetuses) compared to 7.3% (6/82 live fetuses) in the C57 strain. The SWV strain also had a significant increase in the number of dead or resorbed fetuses compared with the control group. No such increase occurred in the C57 strain.

Using the SWV strain, the most susceptible period of gestation was determined by three consecutive ip injections of the racemic mixture (total dose of 1728 mg/kg; 3 doses of 576 mg/kg over 36 hour period) on Days 7.0, 7.5, and 8.0 up to 9.0, 9.5, and 10.0, increasing in half-day intervals. The results indicate that the most susceptible time period for producing exencephaly was Days 8.0, 8.5, and 9.0. Treatment with 576 mg/kg during this time produced 44% exencephaly (46/105 live fetuses). Subsequently, pregnant females were treated with a total dose of 1209-2592 mg/kg (3 x 403-864 mg/kg over 36 hrs) of either the (S) or (R) enantiomer during Days 8.0, 8.5, and 9.0. No exencephaly was observed at 1701 mg/kg (3 x 567 mg/kg/36hrs) of the (S) enantiomer, and only 18% (10/56 live fetuses) at 2592 mg/kg (3 x 864 mg/kg/36hrs). Using the (R) enantiomer, a dose of 1728 mg/kg (3 x 576 mg/kg/36hrs) produced 50% exencephaly (53/106 fetuses), while a dose of 1554 mg/kg (3 x 518 mg/kg/36hrs) produced 33% (28/84) exencephaly. A dose of 1209 mg/kg (3 x 403 mg/kg/36hrs) was without effect.

NOEL for maternal animals = 864 mg/kg/day

NOEL for offspring = < 1152 mg/kg/day for C57 strain using the racemic mixture, 1209 mg/kg (3 x 403 mg/kg/36hrs) for (R) enantiomer in SWV strain and 1728 mg/kg (3 x 576 mg/kg/36hrs) for (S) enantiomer in SWV strain.

Comments: Non-standard strain of mouse (SWV) used with no indication of susceptibility to known teratogens. Study design not in accordance with OECD guidelines: numbers of pregnant females used was below that recommended by OECD; treatment interval during gestation did not include Days 6-15; animals were dosed twice per day rather than once per day. The route of treatment (ip injection) was not considered to be appropriate because of the potential direct effects of the dosing solution on the uterine muscle. Control animals received only physiological saline rather than an isosmotic solution without the test substance. Also, the route of administration may have confounded the interpretation of the results by circumventing the normal absorption/metabolism/excretion pathway. No data of maternal toxicity (weight gain, feed consumption, or clinical signs

of toxicity) were provided other than mortality. There was no analysis of the dosing solutions.

Reference: Collins, M.D., Scott, W.J., Miller, S.J., Evans, D.A., and Nau, H. (1992). Murine Teratology and Pharmacokinetics of the Enantiomers of Sodium 2-Ethylhexanoate. Toxicol. Appl. Pharmacol. 112:257-265.

(E.) **Teratogenicity/Developmental Toxicity** (Preferred study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Fischer 344 Rats

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Twenty-five pregnant females per group were treated by gavage with 0, 100, 250, or 500 mg/kg 2-ethylhexanoic acid on Days 6 through 15 of gestation and dams euthanatized on Day 21. Body weights and feed consumption were measured twice weekly. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in dams. Fetuses preserved in Bouin's fluid for evaluation of visceral anomalies using Wilson's technique, and in Alizarin Red S for skeletal anomalies.

GLP: YES [X]
NO [ ]

Test Results: No mortality occurred. Body weights and feed consumption were comparable among groups. High-dose dams experienced hypoactivity, ataxia, and audible respiration. The pregnancy rate in the high-dose group (21/25) was slightly below the rate in the other groups (23/25), but this difference was not statistically significant. No differences in terminal maternal body weight was noted. Absolute and relative (to body weight) liver weights in high-dose animals were significantly greater (9%) than in the control group. No embryo-toxic effects were noted. Total implants, preimplantation loss, and viable fetuses were comparable among groups. Fetal body weight of high-dose litters were significantly lower than in the control group. However, differences in weight were less than 10% and were probably influenced by a slightly higher average litter size in high-dose dams (9.3 in high-dose vs 8.4 in controls). There were no significant differences among groups in the incidence of total malformations, malformations by category, or individual malformations. The incidence of dilation of the lateral ventricle of the brain (a visceral variation) was significantly increased in the high-dose pups (21/104 pups or 15/21 litters affected) compared to the control group (3/100 pups or 2/23 litters).

Several skeletal variations such as poorly ossified cervical vertebrae, bilobed thoracic vertebrae, unossified proximal phalanges, unossified metatarsels, or unossified sternebrae occurred primarily in the high-dose group and occasionally in the mid-dose group. Total numbers of visceral or skeletal variations were not significantly altered by treatment, however.

NOEL for maternal animals = 250 mg/kg/day

NOEL for offspring = 100 mg/kg/day

Based on changes in fetal body weight and reduced ossification, fetotoxicity occurred at 500 and 250 mg/kg. There is no evidence of teratogenicity.

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(F.) **Teratogenicity/Developmental Toxicity** (Preferred Study - part of previous study. Note broke out robust information for Fischer Rats and New Zealand Rabbits)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: New Zealand White Rabbits

Test Method (e.g., OECD, others): USEPA TSCA Health Effects Testing Guidelines CFR 798.4900. Similar to OECD Guideline 414. Fifteen pregnant females per group were treated by gavage with 0, 25, 125, or 250 mg/kg 2-ethylhexanoic acid on Days 6 through 18 of gestation and does euthanatized on Day 29. Body weights were measured twice weekly, and feed consumption was measured daily. At necropsy, body weight, liver weight, uterine weight, and the status of implantations were evaluated in does. Fetuses were evaluated for visceral anomalies using the method of Staples. The head of half the pups was preserved in Bouin's fluid for evaluation of cranio-facial anomalies using Wilson's technique. The remaining carcass from all pups was stained with Alizarin Red S for skeletal anomalies.

GLP: YES [X]

NO [ ]

Test Results: One mid-dose and one high-dose animal died on test. In addition, one mid-dose animal aborted prior to term. Both events were considered to be treatment-related. High-dose does experienced hypoactivity, ataxia, and gasping. Body weights and feed consumption of animals in this group were reduced (body weight by 5%, feed consumption by 32%) compared with the control group. No differences in liver weight were observed.

Thickened epithelium and ulceration of the glandular portion of the stomach occurred in high-dose does. No fetal or embryo-toxicity was noted. All groups had comparable numbers of implants and live fetuses, and fetal body weights were comparable among groups. No treatment-related malformations or developmental variations occurred. One fetus in the low-dose group had multiple malformations, but this was not considered to be related to treatment. Visceral or skeletal malformations were observed in an occasional pup, but the incidence was not treatment-related.

NOEL for maternal animals = 25 mg/kg

NOEL for offspring = 250 mg/kg

Comments:

Reference: Hendrickx, A.G., Peterson, P.E., Tyl, R.W., Fisher L.C., Fosnight, L.J., Kubena, M.F., Vrbanic, M.A., and Katz, G.V. (1993). Assessment of the Developmental Toxicity of 2-Ethylhexanoic Acid in Rats and Rabbits. Fundam. Appl. Toxicol. 20:199-209.

(G.) **Teratogenicity/Developmental toxicity** (Additional Study)

Test Substance: 2-Ethylhexanoic acid in corn oil

Test Species/Strain: Female Sprague-Dawley Rats

Test Method (e.g., OECD, others): Mechanistic studies were conducted to investigate the role of maternal hepatic metallothionein (MT) induced in response to administration of 2-ethylhexanoic acid (2EHA) on plasma zinc levels and zinc delivery to the conceptus. In the first experiment, pregnant rats on dietary regimens containing adequate Zn were dosed with 0, 3.1, 6.3, 9.4, or 12.5 mmol/kg (0, 446, 907, 1353, or 1800 mg/kg) 2-ethylhexanoic acid on gestation day (GD) 11.25. Eight hours after dosing, the dams were intubated with radiolabeled Zn. After 10 hours (GD 12.0), the dams were killed and maternal liver MT, radiolabeled zinc distribution and reproductive parameters were assessed. In the second experiment, pregnant rats assigned to dietary regimens containing low, adequate, or supplemental Zn, were intubated with 3.5 mmol 2EHA/kg/day (approximately 500 mg/kg/day in a corn oil vehicle) from gestation days

(GD) 8-15. Dams were killed on GD 16, approximately 18 hours after the last dose. Maternal livers were analyzed for Zn and MT concentrations. Maternal plasma was analyzed for zinc concentrations. Fetal development was also assessed. In the third experiment, pregnant rats were divided into three groups and fed diets as described for the second experiment. The animals were also intubated with 2-ethylhexanoic acid in the same manner as the second experiment. Dams were killed on GD 19 and the fetal parameters were assessed.

The fourth experiment used in vitro embryo culture techniques to explore whether sera from animals dosed with 2-ethylhexanoic acid (9.38 mmol/kg; 1350 mg/kg)was teratogenic, if sera from animals fed diets either marginal or adequate for zinc affected in vitro development of embryos, and if the direct addition of zinc to the sera would prevent the abnormalities from occurring.

GLP: YES [ ]
NO [X]

Test Results: The results of the first of the series of experiments demonstrated that maternal liver MT and Zn concentrations increased at all levels of 2-ethylhexanoic acid administered. The results were statistically significant at the three highest doses administered. Even at the lowest dose, the maternal liver MT and Zn levels were approximately twice those of controls but the results were not statistically significant. Embryonic Zn levels were decreased at the three highest dose levels; the results were statistically significant at the two highest doses administered. The results of the second experiment indicated that 2-ethylhexanoic acid induced hepatic MT and hence sequestered Zn in the maternal liver. Under conditions of zinc stress (marginal Zn in the diet), hepatic induction of MT resulted in lowered plasma Zn levels. The teratogenicity of 2-ethylhexanoic acid (encephalocele, tail defects) was enhanced by dietary Zn deficiency and ameliorated by Zn supplementation. The developmental abnormalities and effect of zinc status from the second experiment were confirmed in GD 19 fetuses from the third experiment. The in vitro development of embryos under conditions resulting in decreased serum Zn (Zn marginal diets alone, Zn marginal diets with 2-ethylhexanoic acid administration, Zn adequate diets with 2-ethylhexanoic acid administration), revealed retarded development of the heart, hind- and forebrain, otic, optic and olfactory systems and fore- and hindlimbs. Direct addition of Zn to the Zn deficient sera (from the conditions described previously) resulted in embryonic development similar to controls. Collectively, these results support the hypothesis that 2-ethylhexanoic acid is causing developmental toxicity indirectly and that developmental toxicity will only occur at dose levels that cause maternal liver toxicity and disrupt Zn metabolism and distribution.

NOEL for maternal animals = Not Determined

LOEL for maternal animals = 446 mg/kg

NOEL for offspring = 446 mg/kg

Comments: The mechanistic studies of 2-ethylhexanoic acid developmental toxicity are of importance since it has been determined that maternal hepatic toxicity is responsible for the adverse fetal outcome. Dose levels of 2-ethylhexanoic acid that do not affect maternal serum Zn concentrations should not cause developmental toxicity. It appears that several thresholds must be overcome before developmental toxicity resulting from 2-ethylhexanoic acid exposure occurs.

The first threshold is the dose of 2-ethylhexanoic acid must be large enough to cause an acute phase response in the maternal liver and induce hepatic MT production. The second threshold is when the dose of 2-ethylhexanoic acid causes enough hepatic toxicity and MT induction to decrease maternal serum Zn concentrations. The third threshold is when the decrease in maternal serum Zn concentrations becomes severe enough to prevent adequate amounts of Zn from reaching the developing conceptus. The presence of these thresholds are critical in the risk assessment process for 2-ethylhexanoic acid since exposure to this material typically is low.

Reference: Taubeneck, M.W., J.Y. Uriu-Hare, J.F. Commisso, A.T. Borschers, L.M. Bui, W.Faber and C.L. Keen. (1996) Maternal Exposure to 2-Ethylhexanoic Acid (EHXA), 2-Ethylhexanol (EHXO), and Valproic Acid (VPA) Results in Alterations in Maternal and Embryonic Zinc Status. Teratology 53(2):p88, Abstract 21.

7.8 Specific Toxicities (Neurotoxicity, Immunotoxicity etc.)

No data available.

7.9 Toxicodynamics, Toxico-Kinetics

Test Substance: [2-^{14}C-hexyl] 2-Ethylhexanoic acid (99.6%; 25 mCi/mmole) in corn oil

Test Species/Strain: Female Fischer 344 Rats

Test Method: Similar to USEPA TSCA Health Effects Testing Guideline (CFR 40 798.7100). Radiolabeled 2-ethylhexanoic acid was administered a) as a single oral gavage at either 100 or 1000 mg/kg; b) after 14 days of oral unlabeled 100 mg/kg; c) topically at either 100 or 1000 mg/kg; and d) by intravenous injection (1 mg/kg). Urine, feces, and blood were collected at various intervals for 96 hours. Urine was analyzed using HPLC to separate radioactive metabolites.

GLP: YES [X]
NO [ ]

Test Results: Approximately 72-75% of the oral dose was excreted in the urine within 24 hours. Little radioactivity (<10%) was excreted after 24 hours. The dose influenced the rate of excretion such that 50% of the radioactivity was excreted in the first 8 hours after the 100 mg/kg dose versus 20% after the 1000 mg/kg dose. Fecal excretion accounted for 7-12% in both cases. Slightly less radioactivity was excreted as either urine (64%) or feces (2%) after intravenous injection. Repeated dosing with unlabeled 2-ethylhexanoic acid altered excretion of radioactivity to approximately 55% in urine and 15% in feces within the first 24 hours. After dermal application, approximately 30% of the dose was excreted in the urine during the first 24 hours followed by an additional 8 or 17% from 24-96 hours for the 100 and 1000 mg/kg doses, respectively. Fecal excretion was 7% regardless of the dose level. Dermal absorption was estimated to be 63-70% relative to intravenous administration.

Blood levels after intravenous injection appear to decay in a triphasic manner with half-lives of 0.19 ± 0.11 hrs, 6.6 ± 3.9 hrs, and 117 ± 47 hrs. After oral administration, peak blood levels were achieved after 15 or 30 minutes, and also declined triphasically with half-lives similar to what had been estimated from intravenous administration (0.32 ± 0.04 hrs, 6.8 ± 3.5 hrs, and 98.2 ± 32.8 hrs). Dermal application resulted in slower absorption with peak blood levels occurring 5.7 ± 0.4 hours after application and a half-life of 3.2 ± 0.1 hr. Elimination was biphasic with half-lives of 4.2 ± 0.2 and 251 ± 135 hrs.

Analysis of urine indicated three major peaks: one as a glucuronide conjugate of 2-ethylhexanoic acid; one as a glucuronide conjugate of hydroxylated and diacid derivatives of 2-ethylhexanoic acid, possibly 2-ethyl-6-hydroxyhexanoic acid and 2-ethyl-1,6-hexanedioic acid; and the last as unmetabolized 2-ethylhexanoic acid. No sulfate derivatives were detected. The percentages of each metabolite changed with the dose and route of administration:

Route	Dose	Percentage Excreted as
Oral	1000 mg/kg	45% glucuronide-2-Ethylhexanoic acid 7% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid
	100 mg/kg (Single)	20% glucuronide-2-Ethylhexanoic acid 14% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 7% unmetabolized 2-Ethylhexanoic acid

Oral	***100 mg/kg***	***12% glucuronide-2-Ethylhexanoic acid***
	(Repeated)	12% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 5% unmetabolized 2-Ethylhexanoic acid
Dermal	1000 mg/kg	17% glucuronide-2-Ethylhexanoic acid 3% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 3% unmetabolized 2-Ethylhexanoic acid
Dermal	100 mg/kg	4% glucuronide-2-Ethylhexanoic acid 9% glucuronide-diacid or hydroxylated 2-Ethylhexanoic acid 2% unmetabolized 2-Ethylhexanoic acid

Comments:

Reference: English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Health and Environment Laboratories, Eastman Kodak Company.

8.0 **Experience with Human Exposure** (Give Full Description of Study Design, Effects of Accidental or Occupational Exposure, Epidemiology)

8.1 **Biological Monitoring** (including clinical studies, case reports, etc.)

A case report of workers employed in Finnish sawmills using a wood preservative containing the sodium salt of 2-EHA has been reported (Kröger, et al., 1990). Use of the wood preservative (26% sodium salt of 2-EHA) was by through-dipping or spray irrigation of the wood followed by drying in a 60°C oven. The spray irrigation methodology recycled the wood preservative solution and used vacuum pressurization in an attempt to reduce exposure. The spray irrigation methodology was more efficient than the through-dipping method for treating wood. Job descriptions included machine stacking, straightening, loading (including working in the oven), working under a crane, working in a crane, and cleaning. Exposure was by the dermal or inhalation route. Sampling from the breathing zones were used to determine air levels for inhalation exposure and patch samples were used to determine dermal exposure. An additional area sample from near the dipping pool was included. Urine samples were collected after the working day until the following morning. Protective clothing ranged from coveralls to street clothes. One worker (of 19) used disposable masks and a few used protective gloves (made of leather or natural rubber). Breathing zone air concentrations ranged from 0.01 (lower detection limit) to 0.70 mg/m^3 (0.0017 to 0.12 ppm). Breathing zone air concentrations from the spray irrigation method were about twice as high as with the through-dipping operation. Patch testing from the outer and inner surface of clothes resulted in a mean of approximately 24 or 7.6 mg 2-EHA deposited per hour, respectively. For comparison, 2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5

ml 2-EHA). Urinary concentrations of 2-EHA ranged from 0.01 to 5.4 mmol 2-EHA/mole creatinine. The highest concentrations of 2-EHA in the urine were found in the samples collected immediately after the work shift, indicating rapid elimination of the material. No urine samples were collected during the work shift. Urinary concentrations correlated linearly with measured air concentrations but not with the amount found on the patch samples from the clothing of the workers. The authors therefore considered inhalation to be the primary route of exposure. The highest urinary concentrations were found in the crane operators that worked above the through-dipping pools and did not have dermal exposure. Assuming a worst-case exposure scenario (8 hour exposure to 0.7 mg/m^3; 0.0007 mg/L), a breathing rate of 20 Liters/8 hour workday, and 100% absorption of inhaled 2-EHA vapor; an internal dose of 0.014 mg 2-EHA would be achieved. Assuming a 60-70 kilogram person, the dose rate would be 2-2.33 x 10^{-4} mg/kilogram body weight/8 hour workday. The lowest NOEL from the animal studies is 100 mg/kg. Therefore, the dose resulting from the worst-case exposure scenario is approximately 430,000-fold lower than the lowest NOEL from the laboratory studies.

Reference: Kröger, S., Liesivuori, J., and A. Manninen (1990) Evaluation of Worker's Exposure to 2-Ethylhexanoic Acid (2-EHA) in Finnish Sawmills. Int. Arch. Occup. Environ. Health, 62:213-216.

9.0 Recommended Precautions, Classification (Use and/or Transportation) and Safety Data Sheets

2-EHA is classified as a Class 8, Packing Group III DOT corrosive material ("causes visible destruction or irreversible alterations in skin tissue of animals" after 4 hours of occluded exposure to 0.5 ml 2-EHA).

10.0 Availability and Reference(s) for Existing Review(s)

APPENDIX A

The reports listed in this Appendix are arranged according to the section to which they refer. For reports that are used in multiple sections as indicated by an asterisk (*), only one copy of the report is included and can be found in the first section heading for which it is referenced.

(*)G.T. Waggy, Union Carbide Chemicals and Plastics Company, Inc.

Waggy, G.T., and Payne, J.R. (1974). Environmental Impact Product Analysis: Acute Aquatic Toxicity Testing (Unpublished report). Union Carbide Project Report 910F44, Union Carbide Chemicals and Plastics Company Inc., South Charleston, WV.

(*)Fassett, D.W. (1955). Toxicity Report (Unpublished report). Eastman Kodak Company.

Topping, D.C. (1987). Acute Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-64). Eastman Kodak Company.

Topping, D.C. (1986). Dermal Corrosivity Test of 2-Ethylhexanoic Acid (Unpublished report TX-86-25). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-75). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Gavage) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-90). Eastman Kodak Company.

Gordon, D.R. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-87-125). Eastman Kodak Company.

Bernard, L.G. (1987). Two-Week Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-129). Eastman Kodak Company.

Gordon, D.R. (1988). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Mouse (Unpublished report TX-88-3). Eastman Kodak Company.

Bernard, L.G. (1987). 90-Day Oral (Dietary Administration) Toxicity Study of 2-Ethylhexanoic Acid in the Rat (Unpublished report TX-87-207). Eastman Kodak Company.

English, J.C., Deisinger, P.J., Perry, L.G., and Guest, D. (1987). Pharmacokinetic Studies with 2-Ethylhexanoic Acid in the Female Fischer 344 Rat (Unpublished report TX-87-173). Eastman Kodak Company.

1. General Information

Id 61789-51-3

Date December 20, 2002

Naphthenic acids, cobalt salt (CA index name)

Naftolite

.

Supporting data for dissociation products:

Acid: Data in the U.S. EPA ECOTOX database from three different studies indicate an 96-h LC50 range for naphthenic acids of 5.6 – 7.1 mg/L for bluegill. The 96-h LC50 for another fish species, the zebra fish (*Danio rerio*), is 16.3 mg/L for naphthenic acids. (ECOTOX Database).

Metal: For cobalt chloride, the 96-h LC50 was 333 mg Co/L for *Cyprinus carpio* (common carp) and 1,406 mg Co/L for *Onchorynchus mykiss* (rainbow trout) (ECOTOX data base).

Supporting data for dissociation products:

Supporting data for dissociation products:

ROBUST SUMMARIES

For

Copper Naphthenate

Copper Naphthenate is a FIFRA Chemical and not sponsored under the HPV Challenge Program. Robust summaries are provided here in support of the existing data for metal carboxylates cobalt and zinc naphthenate.

Prepared by

MorningStar Consulting, Inc.

on behalf of

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

DECEMBER 20, 2002

1.0 SUBSTANCE INFORMATION

Generic Name	:	Copper naphthenate
Chemical Name	:	Naphthenic acids, copper salts
CAS Registry No.	:	1338-02-9
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	Variable
Molecular Weight	:	
Synonyms and Tradenames	:	
References	:	

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value : at °C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value : hPa at °C
Decomposition :
Year :

GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.7 FLASH POINT

Type :
Guideline/method :
Value : °C
Year :

GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Halflife (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.2 STABILITY IN WATER

Type : biotic
Guideline/method :
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Degradation : after at pH and °C
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.2.1 MONITORING DATA

Type of measurement : concentration at contaminated site

Media : ground water
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %
%
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :

Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	Static
Guideline/method	:	FIFRA 72-1
Species	:	Rainbow trout (*Oncorhynchus mykiss*)
Exposure period	:	96 h
NOEC	:	<0.13 mg/L
LC0	:	
LC50	:	0.18 mg/L (95% C.I. = 0.11 – 0.23 mg/L)
LC100	:	0.51 mg/L
Other	:	Slope of dose response curve = 5.6722
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	Yes
Year	:	1992
GLP	:	Yes
Test substance	:	Copper naphthenate, purity = 95.6%
Method	:	Nominal test concentrations: 0.13, 0.23, 0.36, 0.60, and 1.0 mg/L.
Method detail	:	Stock solution was made in acetone. Maximum concentration of acetone in any test vessel was 0.5 ml/L. Temperature = 12 – 13 °C. pH = 7.1 - 7.5
Result	:	Mean measured concentrations averaged 90% of the nominal concentrations.
Remark	:	A similar acute test on the bluegill, *Lepomis macrochirus*, produced an 96-hr LC50 of 3.2 mg/L and an LOEC of 1.6 mg/L. (Collins, M.K. 1992. Copper naphthenate – acute toxicity to bluegill sunfish (Lepomis macrochirus) under static renewal conditions. Springborn Laboratories, Inc. SLI Report 92-3-4147.
Reliability	:	1 (reliable without restriction)
Reference	:	Collins, M.K. 1992. Copper naphthenate – acute toxicity to rainbow trout (*Onchorhynchus mykiss*) under static conditions. Springborn Laboratories, Inc. SLI Report 92-1-4086.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Guideline/method	:	FIFRA 72-2
Species	:	*Daphnia magna*
Exposure period	:	48 hr
NOEC	:	0.12 mg/L
EC0	:	0.12 mg/L
EC50	:	0.34 mg/L (95% C.I. = 0.29 - 0.39 mg/L)
EC100	:	0.86 mg/L
Other	:	Slope of dose-response curve = 7.233
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	Yes
Year	:	1992
GLP	:	Yes
Test substance	:	Copper naphthenate, purity = 95.6%
Method	:	Nominal test concentrations: 0.13, 0.22, 0.36, 0.60, and 1.0 mg/L.
Method detail	:	Stock solution was made in acetone. Maximum concentration of acetone in any test vessel was 0.5 ml/L. Temperature = 19 – 21 °C. pH = 8.2 – 8.4
Result	:	Mean measured concentrations averaged 89% of the nominal

		concentrations.
Remark	:	
Reliability	:	1 (reliable without restriction)
Reference	:	Collins, M.K. 1992. Copper naphthenate – acute toxicity to daphnids (*Daphnia magna*) under static conditions. Springborn Laboratories, Inc. SLI Report 92-2-4096.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:
Guideline/method	:
Species	:
Endpoint	:
Exposure period	:
NOEC	:
LOEC	:
EC0	:
EC10	:
EC50	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Acute single dose
Guideline/Method	:	FIFRA 81-1
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Both male and female
Number of animals	:	10 per dose level (5 male, 5 female)
Vehicle	:	Corn oil
Doses	:	1,000; 3,000; 5,000; 7,000; 9,000; and 10,000 mg/kg
LD50	:	5,800 mg/kg (95% C.I. interval = 4,580 – 7,350 mg/kg)
Year	:	1987
GLP	:	No
Test substance	:	8% copper naphthenate (M-Gard S520)
Method	:	
Method detail	:	
Result	:	All mortalities, except for one, occurred within the first 4 days after dosing. Gross pathology of dead animals showed hemorrhagic lungs, darkened livers, slightly dark to dark kidneys and spleens, and hemorrhagic stomachs

livers, slightly dark to dark kidneys and spleens, and hemorrhagic stomachs and intestines with discolored fluids.

Remark : The acute LD50 for a related compound described as 2% copper naphthenate, solvent was greater than 5,000 mg/kg. One of 10 dosed animals died during the study. Reference: Applied biological Sciences Laboratory, 1985. Laboratory Study No. 2585.

Reliability : 2 (reliable with restrictions). Test substance purity and composition is unknown and does not necessarily represent neat copper naphthenate.

Reference : Lacap, L.F. and G.J. Letizia. 1987. Report on acute oral LD50 in rats using 8% copper naphthenate, F-19273 (M-Gard S520). Wells Laboratories Inc., Study No. L-1527.

5.1.2 ACUTE INHALATION TOXICITY

Type : Acute LC50
Guideline/method : FIFRA 81-3
Species : Rat
Strain : Crl:CD(SD)BR
Sex : Male and female
Number of animals : 5 per sex per treatment
Vehicle : Xylene
Doses : 2.966 mg/L
Exposure time : 4 hr
LC50 : >2.966 mg/L (measured)
Year : 1990
GLP : Yes
Test substance : Copper naphthenate
Method :
Method detail : One group of 10 rats (5 of each sex) was exposed to copper naphthenate at a single chamber concentration of 2.966 mg/L by inhalation (whole-body) over a period of 4 hours. The nominal concentration was 7.524 mg/L. Exposure was followed by an observation period of 14 days. Chamber airflow was 20 L/Min. The mean mass aerodynamic diameter of the particles in the atmosphere was 1.71 µm.
Result : There were no deaths in the study, although treatment-related clinical signs (piloerection, salivation, nasal secretion, lethargy, respiratory distress) were observed on the day of exposure. Body weight gain was slightly reduced in the treated animals. There were no treatment-related macroscopic abnormalities.
Remark :
Reliability : 1 Reliable without restriction.
Reference : Collins, C.J. 1990. Copper naphthenate acute inhalation toxicity study – LC50 rats (4 hour exposure). Hazelton UK. Lab Study No. 6320-769/1.

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :

Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type	:	90-Day dermal toxicity
Guideline/method	:	FIFRA 82-3
Species	:	Rat
Strain	:	Crl:CD®BR
Sex	:	Male and female
Number of animals	:	10 per sex per treatment group
Route of admin.	:	Dermal
Exposure period	:	6 hours per day for 13 weeks
Frequency of treatment	:	Once per day; 5 days per week
Post exposure period	:	None
Doses	:	100, 300, or 1000 mg/kg/day
Control group	:	Yes
NOAEL	:	1000 mg/kg/day (for systemic toxicity)
LOAEL	:	Not determined for systemic toxicity
Other	:	
Year	:	1990
GLP	:	Yes
Test substance	:	Copper naphthenate (9.5% copper; purity not specified)
Method	:	
Method detail	:	Test substance was dissolved in light mineral oil at a concentration of 80% by weight and administered onto the clipped intact dorsal skin of each animal. After application, each test site was wrapped with a gauze binder and the dressing secured with Deriform® tape. At the end of a 6-hour exposure period, the dressings were removed and the test sites were wiped with disposable paper towels moistened with mineral oil. The concurrent control group received the vehicle (mineral oil) on a comparable regimen at a dose volume equal to the amount of vehicle received by the highest dose group.
Result	:	Erythema and edema were observed in all treated groups during the study. The frequency and severity of effects were dose-related. In general, the severity of both findings increased during the initial four weeks of dosing, then decreased. Histopathologic evaluation of the application sites revealed a low incidence of dermal hyperplasia, supportive inflammation and hyperkeratosis in rats at the 300 and 1000 mg/kg/day dose levels. No effects on survival, clinical observations, and other parameters used to evaluate systemic toxicity were apparent at any dose level during the study, thus a dose level of 1000 mg/kg/day was the NOAEL for systemic toxicity.
Remark	:	
Reliability	:	(2) Reliable with restrictions. Purity of test material was not specified.
Reference	:	Tomkins, E.C. 1990. 90-Day dermal study in rabbits with copper naphthenate. WIL Research Laboratories. Lab Study No. WIL-153012.

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	TSCA 40 CFR Part 798.5265
System of testing	:	Ames bacterial/microsomal plate incorporation
Species	:	*Salmonella typhimurium*
Strain	:	TA98, TA100, TA1535, TA1537, TA1538
Test concentrations	:	0.05 to 0.5 mg/plate
Cytotoxic concentr.	:	1.0 mg/plate
Metabolic activation	:	Yes, 0.5 ml of rat liver S9 fraction

Year	:	1988
GLP	:	Yes
Test substance	:	Copper naphthenate (purity and composition unknown)
Method	:	Ames Salmonella Mutagenesis Assay
Method detail	:	Test substance was dissolved in DMSO. Assay was run in triplicate. A negative and four positive controls were included.
Result	:	The test substance did not cause a positive increase in the number of histidine revertant colonies and exhibited similar results to the vehicle control, therefore, it is considered non-mutagenic according to the procedure employed.
Remark	:	
Reliability	:	2 Reliable with restrictions. Test substance purity and composition is unknown and does not necessarily represent neat copper naphthenate.
Reference	:	Desai, L.S., A. Raghupathy, and N. DiGiulio. 1988. Ames bacterial/ microsomal plate incorporation assay. Toxikon Corp., Project No. 88G-0096.

Type	:	Cytogenetics assay (chromosome aberrations)
Guideline/method	:	FIFRA 84-2
System of testing	:	Chinese hamster ovary (CHO) cells
Species	:	Hamster
Strain	:	Chinese
Test concentrations	:	Up to 200 µg/ml in activated system; up to 160 µg/ml in unactivated system
Cytotoxic concentr.	:	Approx. 80 µg/ml without activation; Approx. 60 µg/ml with activation
Metabolic activation	:	Yes, with Aroclor induced S-9 fraction from male Sprague-Dawley rats
Year	:	1990
GLP	:	Yes
Test substance	:	Copper naphthenate (purity and copper composition unknown)
Method	:	
Method detail	:	Acetone was used to dissolve the test substance and as a solvent control. Triethylenemelamine and cyclophosphamide were used as positive controls. Whenever possible, a minimum of 100 metaphase spreads (50 per duplicate flask) were examined and scored for chromatid-type and chromosome-type aberrations.
Result	:	No significant increase in chromosome aberrations was observed in the either the activated or the nonactivated test systems. A marginal increase in the number of aberrations was seen at a concentration of 60 µg/ml in the activated system, but in subsequent testing this was not found to be reproducible at similar and higher concentrations.
Remark	:	
Reliability	:	2 Reliable with restrictions. Test substance purity and composition is unknown.
Reference	:	Putman, D.L and M.J. Morris. 1990. chromosome aberrations in Chinese hamster ovary (CHO) cells – copper naphthenate. Microbiological Associates, Inc. Lab Study No. T9037.337.

Type	:	L5178Y TK+/- Mouse lymphoma mutagenesis
Guideline/method	:	FIFRA 84-2
System of testing	:	Mouse lymphoma assay
Species	:	Mouse
Strain	:	L5178Y TK+/-

Test concentrations	:	Initial assay: 4.2 – 56 µg/ml (nonactivated); 3.2 - 42 µg/ml (S-9 activated) Confirmatory assay: 7.5 – 36 µg/ml (nonactivated); 7.5 - 36 µg/ml (activated)
Cytotoxic concentr.	:	100 µg/ml (100% toxicity)
Metabolic activation	:	Yes, with Aroclor induced S-9 fraction
Year	:	1990
GLP	:	Yes
Test substance	:	Copper naphthenate (purity and copper composition not specified)
Method	:	Clive and Spector, 1975 (Mutation Res. 31:17-29)
Method detail	:	Acetone was used as the solvent for preparing dilutions of the test substance. Both initial assay and a confirmatory assay were conducted with and without metabolic activation.
Result	:	In both the initial and the confirmatory assays, copper naphthenate appeared to be more cytotoxic in the presence of metabolic activation. Copper naphthenate did not induce significant mutagenesis in the absence of activation, but produced a dose-dependent response in mutagenesis in the presence of metabolic activation. Positive results with activation were produced in both the initial assay and the confirmatory assay. Colony sizing data for both assays with activation suggested an increase in the relative proportion of small colonies.
Remark	:	
Reliability	:	2 Reliable with restrictions. Test substance purity and composition is unknown.
Reference	:	Harbell, J.W. 1990. L5178Y TK+/- mouse lymphoma mutagenesis assay with confirmation – copper naphthenate. Microbiological Associates, Inc. Lab Study No. T9037.701.

Type	:	Unscheduled DNA synthesis
Guideline/method	:	FIFRA 84-2; OECD 482
System of testing	:	Rat primary hepatocyte cultures
Species	:	Rat
Strain	:	Sprague-Dawley
Test concentrations	:	0.5 to 50 µg/ml
Cytotoxic concentr.	:	15 µg/ml and above
Metabolic activation	:	No
Year	:	1989
GLP	:	Yes
Test substance	:	Copper naphthenate (purity and copper composition unknown)
Method	:	Williams, G. M. 1977. Carcinogen-induced DNA repair in primary rat liver cell cultures, a possible screen for chemical-carcinogens. Canc. Lett. 1:231-237.
Method detail	:	Test substance was dissolved in acetone. Unscheduled DNA synthesis was assessed on the basis of ^{3}H-thymidine incorporation in the cell.
Result	:	In the range-finding test, the test substance was observed to form precipitates in the culture medium at concentrations of 135 µg/ml and higher. Cells exposed to 15 µg/ml exhibited signs of toxicity (some cells had small and irregularly shaped nuclei). Only nuclei with acceptable morphology were evaluated for UDS. The test article did not cause a significant increase in the mean net nuclear grain counts (i.e., an increase of at least 5 counts over solvent control) at concentrations that were not cytotoxic (0.15 to 5.0 µg/ml). Therefore, the test article gave negative results in the study. All criteria for a valid test were met.
Remark	:	

Reliability	:	2 Reliable with restrictions. Test substance purity and composition is unknown.
Reference	:	Curren, R.D. 1989. Unscheduled DNA synthesis in rat primary hepatocytes – copper naphthenate. Microbiological Associates, Inc. Lab Study No. T9037.380.

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Doses	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Teratology / developmental toxicity
Guideline/method	:	FIFRA 83-3
Species	:	Rat
Strain	:	Sprague-Dawley Crl:CD®BR
Sex	:	Female
Route of admin.	:	Gastric intubation
Exposure period	:	Day 6 through 15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Mating until day 20 of gestation
Doses	:	30, 100, and 300 mg/kg/day
Control group	:	Yes (received 10 mL/kg/day of corn oil)
NOAEL maternal tox.	:	30 mg/kg/day
NOAEL teratogen.	:	100 mg/kg/day
Other	:	LOAEL was 100 mg/kg/day for maternal toxicity (based on clinical signs, reduced food consumption, and reduced body weight)
Other	:	LOAEL for developmental toxicity was 300 mg/kg/day based on a slight increase in postimplantation loss
Other	:	
Year	:	1990
GLP	:	Yes
Test substance	:	Copper naphthenate (9.5% copper; purity not specified)
Method	:	Oral gavage
Method detail	:	Doses were set based on results of a range-finding study. The test substance was dissolved in corn oil and administered by gastric gavage at a dose volume of 10 ml/kg. There were 25 positively mated females in each dose group. Females were sacrificed on day 20 of gestation for a

dose group. Females were sacrificed on day 20 of gestation for a scheduled Cesarean section. The uteri and ovaries were examined and the location and numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Fetuses were weighed, sexed, and examined for external, skeletal and soft tissue malformations and developmental variations.

Result : Evidence of maternal toxicity was found in the 100 and 300 mg/kg/day dose groups, including clinical signs, reduced food consumption, and reduced body weight. Postimplantation loss was slightly increased in the 300 mg/kg/day group due to one female with an entire litter resorption; however, this was the only developmental effect in the study that was considered to be potentially treatment-related.

Remark :

Reliability : 2 Reliable with restrictions. Test substance purity was not specified

Reference : Nemec, M.D. 1990. A developmental toxicity study of copper naphthenate in rats. WIL Research Laboratories, Inc. Lab Study No. WIL-153002.

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

14.0 OTHER INFORMATION

14.1 CARCINOGENICITY

1.0 SUBSTANCE INFORMATION

Generic Name	:	Zinc naphthenate
Chemical Name	:	Naphthenic acids, zinc salts
CAS Registry No.	:	12001-85-3
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$Zn(MRCO_2)(NRCO_2)$ Where, R = alkyl group with a chain length of 0 to 10 carbon atoms, M & N are typically one or two fused rings (usually cyclopentane but occasionally cyclohexane or heptane rings) that may contain one or more alkyl substitutions. The total number of carbon atoms in M or N ranges from about 9 to 25. In some cases, no fused ring is present and M or N may be straight-chain or multiple branched carbon/hydrogen/oxygen molecules.
Additional description	:	This compound is the reaction product of zinc oxide and naphthenic acids, a petroleum refining by-product. Depending on the source of naphthenic acid, this compound may also contain 5 –20% paraffinic hydrocarbons which have a similar distillation range to the carboxylic acids. They cannot be removed by standard chemical processing and are not considered to be impurities, but rather legitimate components of naphthenic acid. Zinc naphthenate may be a viscous liquid containing 8-10% zinc or a solid containing 16% zinc (EPA, 1992).
Molecular Weight	:	Ranges from approximately 381 to 813
Synonyms and Tradenames	:	Fungitrol
References	:	EPA (1992). Drinking water toxicity profiles. U.S. Environmental Protection Agency. Report prepared for Army Medical Research and Development Command, Fort Detrick, Maryland. NTIS No. PB93122406. [Subsequently referenced as EPA, (1992)] EPA (1981). Chemical Hazard Information Profile - Draft Report. Cobalt Naphthenate, CAS No. 61789-51-3. U.S. Environmental Protection Agency, Office of Toxic Substances. 8 p. [Subsequently referenced as EPA, (1981)]

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	The pure form of zinc naphthenate is a cold flowing solid at room temperature. Because this substance is a mixture of many of different compounds, a distinct melting point is not expected. The melting point is the result of the transition from a highly ordered crystal form of a compound to the disordered liquid form. Zinc naphthenate is not expected to have a distinct melting point because it is highly disordered as a solid due to its unique chemical composition.
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	ASTM D86-82
Value	:	116°C initial boiling point (pressure not specified)
Decomposition	:	Yes at 255°C
Year	:	1990
GLP	:	Yes
Test substance	:	Technical grade zinc naphthenate (purity = 97%; 14.3% Zn)
Method	:	
Method detail	:	
Result	:	
Remark	:	Test material was a very viscous liquid (i.e., light brown paste)
Reliability	:	(1) Reliable without restrictions.
Reference	:	Grove, S.L. 1990. Technical grade zinc naphthenate – product chemistry physical and chemical characteristics. Mooney Chemicals, Inc. Laboratory. Laboratory project Identification number F-24044-P.

2.3 DENSITY

Type	:	
Guideline/method	:	ASTM D1475-60 (reapproved 1980)
Value	:	1.118 g/ml at 20°C
Year	:	1990
GLP	:	Yes
Test substance	:	Technical grade zinc naphthenate (purity = 97%; 14.3% Zn)

Method	:	
Method detail	:	
Result	:	
Remark	:	Test material was a very viscous liquid (i.e., light brown paste)
Reliability	:	(1) Reliable without restrictions.
Reference		Grove, S.L. 1990. Technical grade zinc naphthenate – product chemistry physical and chemical characteristics. Mooney Chemicals, Inc. Laboratory. Laboratory project Identification number F-24044-P.

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	<0.1 mm Hg (temperature not specified)
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	Mixture of 84% zinc naphthenate (14.5% Zn) and 16% petroleum hydrocarbon oil (CAS No. 64742-52-5)
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	Product MSDS, Sheperd Chemical Co.

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	1.10 at 20 °C
pH value	:	
Year	:	1990
GLP	:	Yes
Test substance	:	Technical grade zinc naphthenate (purity = 97%; 14.7% Zn)
Method	:	
Method detail	:	Zinc as metal content in octanol was measured using ASTM method D2373-85. Zinc in water was measured by atomic absorption spectroscopy according to ASTM method E885-88.
Result	:	
Remark	:	
Reliability	:	(2) Reliable with restrictions. Test was not conducted at different pH values or in buffered water.
Reference	:	Grove, S.L. 1990. Technical grade zinc naphthenate – product chemistry physical and chemical characteristics. Mooney Chemicals, Inc. Laboratory. Laboratory project Identification number F-24044-P.

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	at °C
pH value	:	
concentration	:	at °C
Temperature effects	:	

Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	>200 °C
Year	:	
GLP	:	
Test substance	:	Mixture of 84% zinc naphthenate (14.5% Zn) and 16% petroleum hydrocarbon oil (CAS No. 64742-52-5)
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	Product MSDS, Sheperd Chemical Co.

3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Halflife (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.2 DISSOCIATION

Type : Dissociation constant determination
Guideline/method : OECD 112
pKa : 7.31 and 9.18 at 20°C
Year : 2002
GLP : Yes
Test substance : Zinc naphthenate (54458-2), lot number 20131MI, received from Aldrich Chemical Company. Clear gold liquid, purity not reported.
Approx. water solubility : 500 mg/L as determined visually in preliminary study
Method : OECD Guideline 112, Dissociation Constants in Water
Method detail : Three replicate samples of zinc naphthenate were prepared at a nominal concentration of 250 mg/L by dissolving 0.0250 grams of test substance in 100 mL of degassed water (ASTM Type II). Each sample was titrated against 0.005 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence points and the titration was carried past the final equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result : Mean (N = 3) pKa values were 7.31 (SD = 0.0131) and 9.18 (SD= 0.0466) at 20°C
Remark : The results indicate that dissociation of the test substance will occur at

environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of naphthenic acids, zinc salts, Wildlife International, Ltd. Study No. 534C-121, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %

%

Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Commercial mixtures of the sodium salts of naphthenic acids have been shown to degrade and mineralize to CO_2 when inoculated with microbial populations indigenous to oil sands tailings. Approximately 50% of the organic carbon was converted to CO_2 over a 24-d period. (Reference: Herman et al. 1994. Biodegradation of naphthenic acids by microbial populations indigenous to oil sands tailings. Can. J. Microbiol. 40:467-477)
Metal: Not applicable
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	Static renewal
Guideline/method	:	FIFRA Guideline 72-1
Species	:	Bluegill sunfish (*Lepomis macrochirus*)
Exposure period	:	96 hr
NOEC	:	1.0 mg a.i./L
LC0	:	
LC50	:	1.5 mg a.i./L (1.1 – 2.0 mg a.i./L)
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	Yes
Year	:	1992
GLP	:	Yes
Test substance	:	Zinc naphthenate, Lot # 24044-P, 98.9% active ingredient. Light brown viscous liquid
Method	:	FIFRA Guideline 72-1, Acute toxicity test for freshwater fish
Method detail	:	The test material was prepared in acetone. Ten fish per test concentration (5 per replicate test vessel, 0.15 grams of biomass per liter) were exposed under static conditions to five concentrations of the test material, control, and solvent control (0.5 mL acetone/L) in soft reconstituted water (hardness 38 mg/L as $CaCO_3$, pH 7.5) at a temperature of 19 - 21ºC. After 48 hours of exposure, all survivi ng fish were transferred to freshly prepared test solutions. This technique was used to maintain dissolved oxygen concentrations at acceptable levels.
Result	:	The mean measured concentrations averaged 94% of the nominal concentrations and were 5.0, 3.1, 1.7, 1.0 and 0.54 mg a.i./L. Complete mortality was observed at 96 hours at the two highest test concentrations. The 96-h LC50 was calculated to be 1.5 mg a.i/L (1.1 – 2.0 mg a.i./L). The NOEC was determined to be 1.0 mg a.i./L based upon sublethal effects (partial loss of equilibrium) seen in surviving fish exposed to 1.7 mg a.i./L.
Remark	:	**Supporting data for dissociation products:** **Acid:** Data in the U.S. EPA ECOTOX database from three different studies indicate an 96-h LC50 range for naphthenic acids of 5.6 – 7.1 mg/L for bluegill. The 96-h LC50 for another fish species, the zebra fish (*Danio rerio*), is 16.3 mg/L for naphthenic acids. (U.S. Environmental Protection Agency. 2002. ECOTOX Database System. Version 2.0. Available: http:/www.epa.gov/ecotox). **Metal:** The bioavailability and resultant aquatic toxicity of zinc is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. Reported 96-h LC50 values for zinc chloride (expressed as zinc) for various species of fish include 0.29 mg Zn/L and 0.42 mg Zn/L for bluegill (*Lepomis macrochirus*); 0.093 – 0.815 mg Zn/L for rainbow trout (*Oncorhynchus mykiss*); 0.45 - 2.25 mg Zn/L for common mirror-colored carp (*Cyprinus carpio*) and 1.70 mg Zn/L for sheepshead minnow (*Cyprinodon variegatus*) (ECOTOX database, 2002). The range of reported 96-h LC50 values (n = 15) for freshwater fish was 0.14 – 0.78 mg Zn/L for tests conducted with zinc chloride or zinc sulfate. (Risk Assessment for Zinc Metal, 2001, draft).
Reliability	:	[1] Reliable without restriction
Reference	:	Collins, M.K., 1992. Zinc Naphthenate – Acute Toxicity to Bluegill Sunfish (*Lepomis macrochirus*) under Static Renewal Conditions. Springborn Laboratories, Inc. final report #92-3-4160, submitted to The Naphthenate

Laboratories, Inc. final report #92-3-4160, submitted to The Naphthenate Council c/o Mooney Chemicals, Inc., Cleveland, Ohio.

Type	:	Static
Guideline/method	:	FIFRA Guideline 72-1
Species	:	Rainbow trout (*Oncorhynchus mykiss*)
Exposure period	:	96 hr
NOEC	:	0.39 mg a.i./L
LC0	:	
LC50	:	1.1 mg a.i./L (0.66 – 1.8 mg a.i./L)
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	Yes
Year	:	1992
GLP	:	Yes
Test substance	:	Zinc naphthenate, Lot # 24044-P, 98.9% active ingredient. Light brown viscous liquid
Method	:	FIFRA Guideline 72-1, Acute toxicity test for freshwater fish
Method detail	:	The test material was prepared in acetone. Ten fish per test concentration (5 per replicate test vessel, 0.21 grams of biomass per liter) were exposed under static conditions to five concentrations of the test material, control, and solvent control (0.5 mL acetone/L) in soft reconstituted water (hardness 38 mg/L as $CaCO_3$, pH 7.4) at a temperature of 12 - 13ºC.
Result	:	The mean measured concentrations averaged 102% of the nominal concentrations and were 3.2, 1.8, 1.1, 0.66 and 0.39 mg a.i./L. Complete mortality was observed at 96 hours at the two highest test concentrations, with 50% mortality at the middle concentration and 0% mortality at the two lowest test concentrations. The 96-h LC50 was estimated by nonlinear interpolation to be 1.1 mg a.i/L (0.66 – 1.8 mg a.i./L). The NOEC was determined to be 0.39 mg a.i./L based upon sublethal effects (darkened pigmentation and partial loss of equilibrium) seen in several fish at the next highest test concentration.
Remark	:	
Reliability	:	[1] Reliable without restriction
Reference	:	Collins, M.K., 1992. Zinc Naphthenate – Acute Toxicity to Rainbow Trout (*Oncorhynchus mykiss*) under Static Conditions. Springborn Laboratories, Inc. final report #92-3-4154, submitted to The Naphthenate Council c/o Mooney Chemicals, Inc., Cleveland, Ohio.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Guideline/method	:	FIFRA Guideline 72-2
Species	:	*Daphnia magna*
Exposure period	:	48 hr
NOEC	:	
EC0	:	
EC50	:	4.6 mg a.i./L (2.6 – 8.2 mg a.i/L)
EC100	:	
Other	:	
Other	:	
Other	:	

Limit test	:	
Analytical monitoring	:	Yes
Year	:	1992
GLP	:	Yes
Test substance	:	Zinc naphthenate, Lot # 24044-P, 98.9% active ingredient. Light brown viscous liquid
Method	:	FIFRA Guideline 72-2, Acute toxicity test for freshwater aquatic invertebrates
Method detail	:	The test material was prepared in acetone. Twenty daphnids (= 24 h old) per test concentration (5 per replicate test vessel) were exposed under static conditions to six concentrations of the test material, control, and solvent control (0.5 mL acetone/L) in fortified well water (hardness 170 mg/L as $CaCO_3$, pH 8.1) at a temperature of 20 – 21ºC.
Result	:	The mean measured concentrations averaged 71% of the nominal concentrations and were 35, 20, 14, 8.2, 4.6 and 2.6 mg a.i./L. Complete immobilization was observed at 48 hours at the four highest test concentrations, with 50% immobilization at the 4.6 mg/L concentration and 0% immobilization at the lowest test concentration. The 48-h EC50 was estimated by nonlinear interpolation to be 4.6 mg a.i/L (2.6 – 8.2 mg a.i./L). The NOEC was determined to be 2.6 mg a.i./L (no immobiliztaion or sublethal effects).
Remark	:	**Data for dissociation products:** **Acid:** A 96-h LC50 of 4.8 mg/L for calcium naphthenate has been reported for the marine copepod, *Nitocra spinipes*. (Bengtsson, B.E. and M. Tarkpea. 1983. The acute aquatic toxicity of some substances carried by ships. Mar. Pollut. Bull. 14:213-214). **Metal:** The bioavailability and resultant aquatic toxicity of zinc is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature. Reported 48-h EC50 values for zinc chloride (expressed as zinc) for *Daphnia magna* include 0.33, 0.52, 0.66 and 0.80 mg Zn/L (ECOTOX database, 2002). For several crustaceans, including *Daphnia magna*, *Ceriodaphnia dubia*, and *Ceriodaphnia reticulata*, reported 48-h EC50 values ranged from 0.068 to 0.86 mg Zn/L, for zinc tested as zinc chloride or zinc sulfate. For *Daphnia magna*, reported EC50 values for zinc powder were 0.15 – 0.5 mg Zn/L . (Risk Assessment for Zinc Metal, 2001, draft).
Reliability	:	[1] Reliable without restriction.
Reference	:	Collins, M.K., 1992. Zinc Naphthenate – Acute Toxicity to Daphnids (*Daphnia magna*) under Static Conditions. Springborn Laboratories, Inc. final report #92-13-4089, submitted to The Naphthenate Council c/o Mooney Chemicals, Inc., Cleveland, Ohio.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:
Guideline/method	:
Species	:
Endpoint	:
Exposure period	:
NOEC	:
LOEC	:
EC0	:
EC10	:
EC50	:

Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The toxicity of naphthenic acids to populations of the freshwater diatom, *Navicula seminulum*, has been measured. The 96-h EC50 for growth ranged from 30.5 – 80.5 mg/L (Academy of Natural Sciences. 1960. Cited in the EPA ECOTOX Database 2002. Available at http:/www.epa.gov/ecotox). **Metal:** The bioavailability and resultant aquatic toxicity of zinc is affected by a variety of factors, including water hardness, pH, dissolved organic carbon and temperature The reported 96-h EC50 for zinc chloride for the green alga *Selenastrum capricornutum* was 0.0447 mg Zn/L, while the reported 72-h EC50 for the marine diatom *Skeletonema costatum* was 0.142 mg Zn/L (ECOTOX database, 2002). For zinc powder, the reported 72-h EC50 value based upon growth rate for *Selenastrum capricornutum* was 0.150 mg Zn/L (Risk Assessment for Zinc Metal, 2001, draft).
Reliability	:	
Reference	:	

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Metal**: Zinc is an essential element in nutrition, and is important in membrane stability, in over 300 enzymes, and in the metabolism of proteins and acids. (WHO, 2001, Environmental Health Criteria 221, Zinc). Absorption of zinc in laboratory animals can vary from 10-40% depending upon nutritional status and other ligands in the diet. Absorbed zinc is mainly deposited in muscle, bone, liver, pancreas, kidney and other organs. The biological half-life of zinc is about 4-50 days in rats, depending on the administered dose (WHO, 2001, Environmental Health Criteria 221, Zinc). Increases in zinc concentration in the bodies of experimental animals exposed to zinc are accompanied by reduced levels of copper, suggesting that some of the signs of toxicity ascribed to zinc may be caused by zinc-induced copper deficiency. Moreover, studies have shown that exposure to zinc alters the levels of other essential metals, including iron. Zinc deficiency in animals is characterized by a reduction in growth and cell replication, adverse reproductive and developmental effects, and reduced immunoresponsiveness. (WHO, 2001, Environmental Health Criteria 221, Zinc).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Limit Test
Guideline/Method	:	
Species	:	Rat (albino)
Strain	:	Sherman-Wistar
Sex	:	Male and female
Number of animals	:	5 of each sex
Vehicle	:	None
Doses	:	Single dose of 5.0 g/kg given to all animals
LD50	:	> 5.0 g/kg
Year	:	1980
GLP	:	
Test substance	:	Fungitrol Zinc 8% fungicide (Lot #LPP 3000-4)
Method	:	Described as similar to that in Federal Hazardous Substances Act regulations in 16 CFR 1500.3.
Method detail	:	One group of ten (5 male and 5 female) albino rats was used. Rats weighed between 200 and 300 grams each. Rats were deprived of food, but not water, overnight before dosing. Animals were dosed by direct administration into the stomach by means of a syringe and dosing needle. Following administration, the animals were allowed food and water *ad libitum* for the 14 day observation period during which rats were observed for signs of toxicity.
Result	:	There were no mortalities. Shortly after dosing, the animals were slightly letharegic and ruffled. They appeared normal after 24 hours. Gross pathological examination revealed nothing remarkable.
Remark	:	**Supporting data for dissociation products:** **Acid:** An oral acute toxicity test with a mixture of naphthenic acids isolated from Athabasca oil sands produced appetite suppression, hepatoxicity and cardiovascular effects with a single dose of 300 mg/kg. (Acute and subchronic toxicity of naphthenic acids from oil sands tailings. Toxicol. Sci. 66:347-355). **Metal:** Acute oral toxicity in rodents exposed to zinc is low, and the level at which zinc produces no adverse effect in rats is approximately 160 mg/kg body weight (WHO, 2001, Environmental Health Criteria 221, Zinc). Of the compounds zinc nitrate, zinc sulfate, zinc chloride and zinc acetate, zinc acetate was the most toxic, with oral LD50 values of 237 mg Zn/kg bw (rat) and 86 mg Zn/kg bw (mouse). The LD50 for zinc chloride in an oral exposure was reported to be 528 mg Zn/kg bw in rats and 605 mg Zn/kg bw in mice (ATSDR, 1994, Toxicological Profile for Zinc).
Reliability	:	[2] Reliable with restrictions. Basic data given: comparable to guidelines.
Reference	:	Biosearch, Inc. (1980). Fungitrol Zinc 8% Toxicological Studies. Project number 80-2171A. Submitted to Tenneco Chemicals. [Available from the National Technical Information Service in microfiche OTS05151131, „Eight toxicological studies of naphthenic acids, zinc salts with attachments and cover letter dated 072187“][Subsequently referenced as Biosearch (1980)]

Type	:	Limit test
Guideline/Method	:	Oral Toxicity Single Dose, EPA 40 CFR 163.81-1 (Proposed)
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Five males and five females, weighing 200 – 300 grams each
Number of animals	:	10
Vehicle	:	

Doses	:	Single dose of 5 g/kg administered to all animals
LD50	:	> 5 g/kg
Year	:	1985
GLP	:	No
Test substance	:	2% zinc naphthenate, in mineral spirits solvent. Sample density 0.82 g/mL
Method	:	Oral Toxicity Single Dose, EPA 40 CFR 163.81-1 (Proposed)
Method detail	:	Food (but not water) withheld 24 hours prior to dosing. Following dosing by gavage, food and water allowed *ad libitum*. Animals observed twice daily for 14 days, weight recorded after 7 and 14 days. All animals autopsied.
Result	:	Lethargy, piloerection and nasal discharge were observed in some animals following intubation. 1/5 females and 0/5 males died (death at 30 hours following intubation). All surviving animals appeared normal at 48 hours and no abnormal behavioral or physical symptoms were observed during the remainder of the observation period. Hemhorragic lungs, dark kidneys and pale spleen in the dead animal; all other animals had normal tissues and organs at autopsy.
Remark	:	
Reliability	:	[2] Reliable with restriction. Basic data given, comparable to guidelines. Limited description of test substance.
Reference	:	Hoster, S., 1985. Acute Toxicology – Oral, 2% Zinc Naphthenate in Mineral Spirits Solvent, Applied Biological Sciences Laboratory, prepared for Mooney Chemicals Inc.

Type	:	Oral LD50
Guideline/Method	:	
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	Stoddard-type solvent
Doses	:	
LD50	:	> 6.0 g/kg
Year	:	
GLP	:	
Test substance	:	Zinc naphthenate containing 8.0% zinc
Method	:	Smyth & Carpenter (1944)
Method detail	:	Dosing by gavage
Result	:	
Remark	:	This LD50 is equivalent >400 mg Zn/kg. As measured by the LD50, the zinc salt was similar in toxicity to the calcium (>6.0 g/kg), copper (>6.0 g/kg), and manganese (>6.0 g/kg) salts of naphthenic acid. It was more toxic than the cobalt (>6.0 g/kg) and lead (5.1 g/kg) salts of naphthenic acid, and a naphthenic acid fraction derived from crude kerosene acids (3.0 g/kg) that were also tested. A phenyl mercury naphthenate (10% Hg) was considerably more toxic than all of these compounds with an LD50 of 0.39 g/kg.
Reliability	:	[4] Not reliable. Documentation insufficient for assessment.
Reference	:	Rockhold, W.T. 1955. Toxicity of naphthenic acids and their metal salts. A.M.A. Arch. Indust. Health. 12: 477-482.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	Limit test
Guideline/method	:	
Species	:	Rat (albino)

Strain	:	
Sex	:	Male and female
Number of animals	:	5 of each sex
Vehicle	:	Mineral spirits
Concentrations	:	A single concentration of 11.6 mg/L was administered to all animals
Exposure time	:	4 hr
LC50	:	>11.6 mg/L (for a 50% w/v suspension in mineral spirits)
Year	:	1980
GLP	:	Yes (per EPA's proposed GLP regulations at the time)
Test substance	:	Fungitrol Zinc 8% fungicide (Lot #LPP 3000-4)
Method	:	Similar to that proposed in 40 CFR 163.81-3 (August 22, 1978).
Method detail	:	Animals were exposed to an aerosol of the test material inside a 260 liter plexiglass exposure chamber for four hours (flow rate of 20 L per minute). Following the exposure period, animals were returned to their cages and observed for a 14-d period. Signs of toxicity and mortalities were noted. The aerosol was generated by a six jet Collision nebulizer. Particle size of the aerosol was determined using an Andersen Sampler cascade impactor. The mass median diameter of particles was 0.54 µm, within the respirable range. The concentration of particles was 0.42 mg/L.
Result	:	There were no mortalites of exposed animals. Animals appeared depressed and ruffled within 18 to 24 hours after exposure, but returned to normal after 48 hours. Gross pathological examination revealed nothing remarkable.
Remark	:	**Supporting data for dissociation products:** **Metal:** Zinc chloride is a primary ingredient in smoke bombs, resulting in respiratory injury. In a 10-minute inhalation study with rats, zinc chloride aerosol was lethal at concentrations as low as 940 mg Zn/m3 (Risk Assessment for Zinc Metal, 2001, draft).
Reliability	:	[2] Reliable with restrictions. Basic data given: comparable to guidelines.
Reference	:	Biosearch, Inc. (1980).
Type	:	Limit test
Guideline/method	:	Inhalation toxicity – EPA (40 CFR 163.81-3)
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Male and female, weighing 200 – 300 grams each
Number of animals	:	5 of each sex for the exposure, 5 of each sex for the control
Vehicle	:	Mineral spirits
Concentrations	:	A single concentration (25.2 mg/L nominal, 0.72 mg/L assayed) was administered to all animals.
Exposure time	:	4 hr
LC50	:	
Year	:	1985
GLP	:	No
Test substance	:	2% zinc naphthenate in mineral spirits solvent
Method	:	Inhalation toxicity - EPA (40 CFR 163.81-3)
Method detail	:	Animals were exposed to an aerosol of the test material inside a 392 liter plexiglass exposure chamber for four hours (flow rate 20 L/min.). Sample (1000 g) was sprayed into the chamber with a Burgess Thermo Model F-982. Sample was sprayed for 15 seconds at 5 minute intervals for the first 15 minutes and then 5 seconds at 5 minute intervals for the remaining time. Following the exposure period, animals were returned to their cages and observed twice daily for a 14-d period. Signs of toxicity and mortalities were noted, and weights taken at 2,3,4 and 7 days. A group of 10 rats was held for a two week observation period under the same conditions. Particle size of the aerosol was determined using an Andersen Sampler, with 87-88% of

of the aerosol was determined using an Andersen Sampler, with 87-88% of the particles 9-10 µm or larger.

Result : There were no mortalites of exposed animals. Animals appeared normal at the end of the exposure period and for the duration of the observation period. Autopsies indicated one exposed animal and one control animal with hypervacuolization of the center of the right kidney; all other tissues and organs appeared normal.

Remark :

Reliability : [2] Reliable with restriction. Basic data given, comparable to guidelines. Limited description of test substance.

Reference : Hoster, S., 1985. Acute Toxicology – Inhalation, 2% Zinc Naphthenate in Mineral Spirits Solvent, Applied Biological Sciences Laboratory, prepared for Mooney Chemicals Inc.

5.1.3 ACUTE DERMAL TOXICITY

Type : Limit test

Guideline/method :

Species : Rabbit (albino)

Strain :

Sex : Male and female

Number of animals : 5 of each sex

Vehicle : None

Doses : A single dose of 2.0 g/kg was administered to all animals.

LD50 : >2.0 g/kg

Year : 1980

GLP : Yes (per EPA's proposed GLP regulations at the time)

Test substance : Fungitrol Zinc 8% fungicide (Lot #LPP 3000-4)

Method : Similar to that proposed in 40 CFR 163.81-2 (August 22, 1978).

Method detail : Animals weighed between 2.0 and 3.0 kg. All animals had their backs clipped free of hair 24 hours prior to testing. All animals had their backs abraded prior to dosing. Test material was applied to the back of each animal and covered with a large gauze patch. An impervious material was then wrapped snugly around the trunk of each animal. The dressings were removed after 24 hours and any excess test material was removed. Animals were observed for a period of 14 days for signs of toxicity.

Result : There were no mortalities in the test. Very substantial skin irritation was noted throughout the observation period, but no other untoward symptoms were observed. Gross pathological examination of all survivors revealed nothing remarkable.

Remark : **Supporting data for dissociation products:**
Metal: Zinc chloride is reported to cause moderate to severe skin irritation in the rabbit, guinea pig and mouse at 0.48 mg Zn/cm2 while zinc acetate at 7.2 mg Zn/cm2 was reported to be irritating to the rabbit and mouse but caused no effects in the guinea pig (ATSDR, 1994, Toxicological Profile for Zinc).

Reliability : [2] Reliable with restrictions. Basic data given: comparable to guidelines.

Reference : Biosearch, Inc. (1980).

Type : Limit test

Guideline/method : Dermal Toxicity – EPA (40 CFR 163.81-2)

Species : Rabbit (albino)

Strain : New Zealand

Sex : Male and female

Number of animals : 5 of each sex (exposed); 5 of each sex (untreated control)

Vehicle	:	None
Doses	:	A single dose of 2.0 g/kg was administered to all animals.
LD50	:	>2.0 g/kg
Year	:	1985
GLP	:	No
Test substance	:	2% zinc naphthenate, in mineral spirits solvent. Sample density 0.83 g/mL
Method	:	Dermal Toxicity – EPA (40 CFR 163.81-2)
Method detail	:	The trunks of the animals were clipped free of hair and abraded prior to dosing. An impervious sleeve was wrapped around the trunk and the dose introduced under the sleeve. At the end of 24 hours, the sleeve was removed, skin reactions noted, and any excess test material removed. Animals were observed for a period of 14 days for signs of toxicity. Weight changes were recorded at 7 days. Gross pathology performed at study termination.
Result	:	There were no mortalities in the test. All exposed animals exhibited slight erythema at 24 hours and 48 hours. By 72 hours, only 3 animals showed slight erythema and by day 7 all signs of irritation had subsided. No edema was observed. One animal showed weight loss and one showed diarrhea. No other untoward symptoms were observed. Gross pathological examination indicated congested spleen in 2 exposed animals, pale thin spleen in one exposed animal, streak in the liver in one exposed animal, and an abscess under the skin in one animal. All other organs and tissues appeared normal; four autopsied control animals demonstrated normal pathology.
Remark	:	
Reliability	:	[2] Reliable with restriction. Basic data given, comparable to guidelines. Limited description of test substance.
Reference	:	Hoster, S., 1985. Acute Toxicology – Dermal, 2% Zinc Naphthenate in Mineral Spirits Solvent, Applied Biological Sciences Laboratory, prepared for Mooney Chemicals Inc.

5.2.1 SKIN IRRITATION

Type	:	Primary skin irritation
Guideline/method	:	
Species	:	Rabbit (albino)
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	0.5 ml of undiluted test material
Exposure time	:	24 hr
Number of animals	:	Six
Vehicle	:	None
Classification	:	Study 1: primary skin irritant; Study 2: skin irritant
Year	:	1980
GLP	:	Yes (per EPA's proposed GLP regulations at the time)
Test substance	:	Fungitrol Zinc 8% fungicide (Lot #LPP 3000-4)
Method	:	Similar to that proposed in 40 CFR 163.81-5 (August 22, 1978).
Method detail	:	The test was conducted twice. After clipping, a 0.5 ml sample of the test material was applied to areas of intact and abraded skin on six albino rabbits for a period of 24 hours. Test material was held in place by gauze patches secured with an impervious material wrapped around the torso of each animal. Examination and scoring (Draize method) for erythema, eschar, and edema was conducted at 24 and 72 hours.
Result	:	Results were similar for both intact and abraded skin and at both time

points. Scores were similar for the primary endpoints. The primary irritation scores were 6.29 and 4.29 for the first and second tests, respectively.

Remark : **Supporting data for dissociation products:**
Metal: Zinc chloride, applied daily as a 1% aqueous solution in an open patch test for 5 days, was severely irritant in rabbits, guinea pigs and mice, inducing epidermal hyperplasia and ulceration. Aqueous zinc acetate (20%) was slightly less irritating. (WHO, 2001, Environmental Health Criteria 221, Zinc).

Reliability : [2] Reliable with restrictions. Basic data given: comparable to guidelines.

Reference : Biosearch, Inc. (1980).

Type : Primary skin irritation
Guideline/method : Skin Irritation Test – EPA (40 CFR 163.81-5)
Species : Rabbit (albino)
Strain : New Zealand
Sex : Not specified
Concentration :
Exposure : 0.5 ml of undiluted test material
Exposure time : 24 hr
Number of animals : Six
Vehicle :
Classification : Slight irritation at 72 hours but subsided by 96 hours
Year : 1985
GLP : No
Test substance : 2% zinc naphthenate, solvent.
Method : Skin Irritation Test – EPA (40 CFR 163.81-5)
Method detail : The trunk of each animal was clipped free of hair. After clipping, a 0.5 ml sample of the test material was applied to two areas of intact and two areas of abraded skin on six albino rabbits for a period of 24 hours. Test material was held in place by gauze patches secured with an impervious material wrapped around the torso of each animal. Examination and scoring for erythema, eschar, and edema was conducted at 24, 72 and 96 hours.

Result : At 24 hours, no erythema was observed but two animals had slight to moderate edema on abraded skin. At 72 hours, 5 animals exhibited slight erythema but no animals exhibited edema. By 96 hours, all signs of irritation had subsided.

Remark :

Reliability : [2] Reliable with restriction. Basic data given, comparable to guidelines. Limited description of test substance.

Reference : Hoster, S., 1985. Acute Toxicology – Skin Irritation, 2% Zinc Naphthenate in Mineral Spirits Solvent, Applied Biological Sciences Laboratory, prepared for Mooney Chemicals Inc.

5.2.2 EYE IRRITATION

Type : Primary eye irritation
Guideline/method :
Species : Rabbit (albino)
Strain : New Zealand White
Sex : Not specified
Concentration :
Dose : 0.1 ml of undiluted test material
Exposure time :
Number of animals : Six
Vehicle : None

Classification	:	Not a primary ocular irritant
Year	:	1980
GLP	:	Yes (per EPA's proposed GLP regulations at the time)
Test substance	:	Fungitrol Zinc 8% fungicide (Lot #LPP 3000-4)
Method	:	Similar to that proposed in 40 CFR 163.81-4 (August 22, 1978).
Method detail	:	A 0.1 ml sample of the material was instilled into the right eyes of six adult rabbits. Left eyes were untreated and served as controls. The test material was not washed from the eyes. The treated eyes were examined and scored according to Draize scale at one, two, three, five, and seven days following instillation of the test material.
Result	:	Total ocular irritation scores ranged from 4 to 8 (avg. = 7.0) for individual animals at 24 hours after instillation. Total ocular irritation scores were zero for all animals at all subsequent time points.
Remark	:	
Reliability	:	[2] Reliable with restrictions. Basic data given: comparable to guidelines.
Reference	:	Biosearch, Inc. (1980).

Type	:	Primary eye irritation
Guideline/method	:	Skin Irritation Test – EPA (40 CFR 163.81-4 proposed)
Species	:	Rabbit (albino)
Strain	:	
Sex	:	Not specified
Concentration	:	
Dose	:	0.1 ml of undiluted test material
Exposure time	:	
Number of animals	:	Nine (6 exposed and 3 control)
Vehicle	:	None
Classification	:	Not an irritant
Year	:	1985
GLP	:	No
Test substance	:	2% zinc naphthenate, solvent.
Method	:	Skin Irritation Test – EPA (40 CFR 163.81-4 proposed)
Method detail	:	A 0.1 ml sample of the material was instilled into the right eyes of six adult rabbits. In these six animals, the test material was not washed from the eyes. Left eyes were untreated and served as controls. In three other adult rabbits, the test material was instilled in the same manner but each eye was subsequently flushed with lukewarm water no sooner than 20-30 seconds after instillation. The treated eyes were examined and scored for damage to the cornea, iris and conjunctiva at 1, 2, 3, 4 and 7 days after treatment.
Result	:	All ocular irritation scores were zero at all time points. No irritation was observed.
Remark	:	
Reliability	:	[2] Reliable with restriction. Basic data given, comparable to guidelines. Limited description of test substance.
Reference	:	Hoster, S., 1985. Acute Toxicology – Eye Irritation, 2% Zinc Naphthenate in Mineral Spirits Solvent, Applied Biological Sciences Laboratory, prepared for Mooney Chemicals Inc.

5.4 REPEATED DOSE TOXICITY

Type	:	90-day dermal toxicity
Guideline/method	:	FIFRA 82-3 and OECD 411
Species	:	Rabbit
Strain	:	New Zealand white
Sex	:	Male and female

Number of animals	:	10 of each sex per treatment group
Route of admin.	:	Dermal
Exposure period	:	6 hours per day for 13 weeks
Frequency of treatment	:	Once per day; 5 days per week for 13 weeks
Post exposure period	:	None
Doses	:	100, 300, and 1000 mg/kg/day
Control group	:	Yes
NOAEL	:	300 mg/kg/day excluding dermal irritation as an endpoint
LOAEL	:	1,000 mg/kg/day excluding dermal irritation as an endpoint
Other	:	Dermal irritation was present at the application site in all groups, including control. Irritation increased in a dose-related manner.
Year	:	1990
GLP	:	Yes
Test substance	:	Technical grade zinc naphthenate (Purity = 98.9%; 14.3% zinc)
Method	:	
Method detail	:	Test substance was dissolved in light mineral oil at a concentration of 50% by weight and administered onto the clipped intact dorsal skin (right flank) of each animal. After application, each test site was wrapped with a gauze binder and the dressing secured with Deriform® tape. At the end of a 6-hour exposure period, the dressings were removed and the test sites were wiped with disposable paper towels moistened with mineral oil. The concurrent control group received the vehicle (mineral oil) on a comparable regimen at a dose volume equal to the amount of vehicle received by the highest dose group.
Result	:	No treatment-related clinical signs or effects on mortality were apparent in the study; however, dermal irritation (including moderate and severe grades of erythema and edema, as well as fissuring) was observed in a dose-related manner. Severe signs of skin irritation such as eschar and blanching were not observed. A tolerance developed to the irritating effects of the test substance and the incidences of severe edema, erythema and fissuring were lower during the final weeks of the study. Histopathologic evaluation of the application sites revealed treatment-related lesions characterized by hyperkeratosis of the epidermal surface and dermal hyperplasia. Body weight means of both male and female rabbits in the 1000 mg/kg/day group were lower than control means throughout the study. Relative mean kidney and adrenal weights of the high dose group's animals were significantly above the control mean. No treatment-related effects were apparent in the serum chemistry values. A slight increase in neuturophils in the high dose group was the only alteration in clinical pathological parameters indicative of a treatment-related effect.
Remark	:	
Reliability	:	(1) Reliable without restrictions.
Reference	:	Tomkins, E.C. 1990. 90-Day dermal study in rabbits with zinc naphthenate. WIL Research Laboratories. Lab Study No. WIL-153006.

Type	:	Contact dermal irritation / Sensitization
Guideline/method	:	
Species	:	Guinea pig (albino)
Strain	:	
Sex	:	Male
Number of animals	:	10
Route of admin.	:	Dermal
Exposure period	:	See method details below
Frequency of treatment	:	See method details below
Post exposure period	:	See method details below

Dose	:	0.5 ml of 10% w/v suspension in mineral spirits
Control group	:	None
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	1980
GLP	:	Yes (per EPA's proposed GLP regulations at the time)
Test substance	:	Fungitrol Zinc 8% fungicide (Lot #LPP 3000-4)
Method	:	
Method detail	:	A 0.5 ml sample of test material was applied to intact skin test sites on 10 guinea pigs. A gauze patch was used to hold the test substance in place. After a 24-hour contact period, the patch was removed and the animals were allowed to rest for one day. Following the rest period, another application was applied to the same skin site using a fresh sample. This sequence was repeated for a total of ten induction applications. After the tenth application, the animals were rested for a two-week period. Following this period, a challenge application was placed at skin sites differing from the original test sites. The challenge application was removed after 24 hours. Sites were examined for irritation using the Draize scale 24 hours after each induction application, and 24 and 48 hours after the challenge application.
Result	:	The test material produced well defined erythema and very slight edema during the induction period. Similar or slightly less severe effects were noted after the challenge dose. Based on study results, the test material appeared to be a primary skin irritant and fatiguing agent, and possibly a sensitizing agent in the guinea pig.
Remark	:	**Supporting data for dissociation products:** **Metal:** Long-term oral exposure to zinc indicates the target organs of toxicity to be the hematopoeitic system in rats, ferrets and rabbits; the kidney in rats and ferrets; and the pancreas in mice and ferrets (WHO, 2001, Environmental Health Criteria 221, Zinc). The daily oral administration of zinc chloride to rats in water over a 4 week period produced a LOAEL of 12 mg Zn/kg/d, based upon hematological effects. Zinc acetate given to rats in water over three months yielded NOAEL values of 95 to 191 mg Zn/kg/d. During a 13-week exposure to zinc sulfate via the diet, NOAEL values for the rat ranged from 53 to 565 mg Zn/kg/day and for the mouse were 104 mg Zn/kg/d, based upon various parameters. (ATSDR, 1994, Toxicological Profile for Zinc).
Reliability	:	[2] Reliable with restrictions. Basic data given: comparable to guidelines.
Reference	:	Biosearch, Inc. (1980).

Type	:	Subchronic oral
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Dose	:	
Control group	:	
NOAEL	:	
LOAEL	:	

Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: An oral 90-d subchronic toxicity test with a mixture of naphthenic acids (sodium salts) isolated from Athabasca oil sands produced significant physical, clinical, and pathological changes at a dose level of 60 mg/kg/day (5 doses per week). No significant adverse effects were seen at a dose level of 6 mg/kg/day. Several parameters suggested that the liver was the primary target organ in this study. Liver weight was increased 35% above control values in the high dose group. Body weight gain was also reduced 8-9% in this exposure group compared to controls. (Rogers et al. 2002. Acute and subchronic toxicity of naphthenic acids from oil sands tailings. Toxicol. Sci. 66:347-355).

Metal: Long-term oral exposure to zinc indicates the target organs of toxicity to be the hematopoeitic system in rats, ferrets and rabbits; the kidney in rats and ferrets; and the pancreas in mice and ferrets (WHO, 2001, Environmental Health Criteria 221, Zinc). The daily oral administration of zinc chloride to rats in water over a 4 week period produced a LOAEL of 12 mg Zn/kg/d, based upon hematological effects. Zinc acetate given to rats in water over three months yielded NOAEL values of 95 to 191 mg Zn/kg/d. During a 13-week exposure to zinc sulfate via the diet, NOAEL values for the rat ranged from 53 to 565 mg Zn/kg/day and for the mouse were 104 mg Zn/kg/d, based upon various parameters. (ATSDR, 1994, Toxicological Profile for Zinc).
Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type : L5178Y (TK+/TK-) Mouse lymphoma mutagenesis
Guideline/method : FIFRA 84-2
System of testing : Suspension / plate
Species : Mouse
Strain : L5178Y (TK+/TK-)
Test concentrations : Initial assay: 1.3 to 100 µg/ml;
Confirmatory assay: 7.5 to 75 µg/ml
Cytotoxic concentr. : 100 µg/ml for nonactivated cultures; 1000 µg/ml for activated cultures
Metabolic activation : Rat liver S-9 fraction, induced with Aroclor 1254
Year : 1990
GLP : Yes
Test substance : Technical grade zinc naphthenate (Purity = 98.9%; 14.3% Zn)
Method : Clive and Spector, 1975 (Mutation Res. 31:17-29)
Method detail : Ethanol was used as the solvent for preparing dilutions of the test substance.
Result : Positive findings (mutant frequencies at least twice the frequency of the controls), both with and without metabolic activation, were found in the initial and confirmatory assays. A dose-dependent response was seen in the treated cultures both with and without metabolic activation. Colony sizing data indicated an increase in the proportion of small mutant colonies from cultures treated with the test substance, suggesting that it may show

cultures treated with the test substance, suggesting that it may show clastogenic activity. All criteria for a valid test were met.

Remark : **Supporting data for zinc naphthenate:**
Zinc naphthenate at concentrations of 0.0033 – 0.04 µl/ml with activation and 0.010 – 0.033 µl/ml without activation produced positive results in the L5178Y TK+/- mouse lymphoma mutagenesis assay. The zinc content and purity of the test substance in this test is unknown. (Reference: Short-term test program sponsored by the Division of Cancer Etiology, National Cancer Institute, Dr. David Longfellow, Project Officer. Cited in Chemical Carcinogenesis Research Information System, National Library of Medicine:

Supporting data for similar salts:
Similar mouse lymphoma tests with the calcium and copper salts of naphthenic acids were also positive both with and without metabolic activation. However, copper naphthenate produced negative results in the Ames Assay with *Salmonella typhimurium* both with and without metabolic activation. (Reference: Short-term test program sponsored by the Division of Cancer Etiology, National Cancer Institute, Dr. David Longfellow, Project Officer. Cited in Chemical Carcinogenesis Research Information System, National Library of Medicine: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?CCRIS)

Supporting data for dissociation products:
Metal: In 11 separate in vitro studies with zinc chloride or zinc sulfate, negative results were reported with the exception of two ambiguous results and one weakly positive result. (Risk Assessment for Zinc Metal, 2001, draft).

Reliability : (1) Reliable without restrictions.

Reference : Harbell, H.W. 1990. L5178Y TK+/- mouse lymphoma mutagenesis assay with confirmation – test article zinc naphthenate. Microbiological Associates, Inc. Lab Study No. T9036.701.

Type : Unscheduled DNA Synthesis
Guideline/method : FIFRA 84-4
System of testing : Primary hepatocytes
Species : Rat
Strain : Harlan Sprague-Dawley
Test concentrations : 0.015 to 35 µg/ml (8 dose levels)
Cytotoxic concentr. : 15 µg/ml
Metabolic activation : No
Year : 1989
GLP : Yes
Test substance : Technical grade zinc naphthenate (Purity = 98.9%; 14.3% Zn)
Method : Williams, 1979 (In Chemical Mutagens, Vol. VI, DeSerres, F.J. and A. Hollander, eds., Plenum Press, pp 61-79)
Method detail : Ethanol was used to dissolve the test substance and as a solvent control. DMBA was used as a positive control. A parallel cytotoxicity test was conducted to determine the relative toxicity of the test substance.
Result : The test substance did not cause a significant increase in unscheduled DNA synthesis as measured by the mean number of net nuclear grain counts at any dose level. All criteria for a valid test were met.
Remark :
Reliability : (1) Reliable without restriction.
Reference : Curren, R.D. 1989. Unscheduled DNA synthesis in rat primary hepatocytes - test article zinc naphthenate. Microbiological Associates, Inc. Lab Study No. T9036.380.

Lab Study No. T9036.380.

Type	:	Chromosome aberration assay
Guideline/method	:	FIFRA 84-2
System of testing	:	Chinese hamster ovary cells
Species	:	Hamster
Strain	:	Chinese
Test concentrations	:	Initial assay: 5 to 80 µg/ml for nonactivated cultures;10 to 160 µg/ml for activated cultures; Confirmatory assay: 80 to 200 µg/ml for nonactivated cultures; 60 to 140 µg/ml for activated cultures
Cytotoxic concentr.	:	80 µg/ml
Metabolic activation	:	Yes, with Aroclor induced S-9 fraction from male Sprague-Dawley rats
Year	:	1990
GLP	:	Yes
Test substance	:	Technical grade zinc naphthenate (Purity = 98.9%; 14.3% Zn)
Method	:	
Method detail	:	Ethanol was used to dissolve the test substance and as a solvent control. Triethylenemelamine and cyclophosphamide were used as positive controls. Whenever possible, a minimum of 100 metaphase spreads (50 per duplicate flask) were examined and scored for chromatid-type and chromosome-type aberrations.
Result	:	Zinc naphthenate produced positive results in the CHO cytogenetics assay. Toxicity was a limiting factor in the analysis of test concentrations in both the nonactivated and S-9 activated studies. The percentage of cells with structural chromosome aberrations was significantly increased, in a dose-responsive manner, at all test concentrations analyzed for both the S-9 activated and the nonactivated test systems.
Remark	:	
Reliability	:	(1) Reliable without restriction.
Reference	:	Putman, D.L. and M.J. Morris. 1990. Chromosome aberrations in Chinese hamster ovary (CHO) cells - test article zinc naphthenate. Microbiological Associates, Inc. Lab Study No. T9036.337.

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Doses	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Metal:** Studies on the induction of chromosome aberrations in bone marrow cells harvested from animals exposed to zinc yield equivocal results. Increased aberrations have been seen in rats after oral exposure to zinc chloride in water (249 mg/L for 14 days) and in mice given intraperitoneal injections of zinc chloride (2-5 mg/kg as zinc chloride). In

intraperitoneal injections of zinc chloride (2-5 mg/kg as zinc chloride). In contrast, other studies have produced negative findings or have suggested that the induction of aberrations is contingent upon concomitant calcium deficiency. Negative results have been reported in the mouse micronucleus test (i.p. injection of zinc sulfate) and in the dominant lethal mutation assay with mice (i.p. injection of zinc chloride at 15 mg/kg). (WHO, 2001, Environmental Health Criteria 221, Zinc).

Reliability :

Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Teratology / developmental toxicity
Guideline/method	:	
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Female
Route of admin.	:	Oral
Exposure period	:	Day 6 through 15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Mating until day 20 of gestation
Doses	:	94, 188, and 938 mg/kg/day
Control group	:	Yes (received 3.75 mL/kg/day of corn oil)
NOAEL maternal tox.	:	188 mg/kg/day
NOAEL teratogen.	:	188 mg/kg/day
Other	:	LOAEL was 938 mg/kg/day for maternal toxicity
Other	:	LOAEL was 938 mg/kg/day for toxicity to fetuses
Other	:	
Year	:	1991
GLP	:	Yes
Test substance	:	Zinc naphthenate, technical, containing 13.7% zinc. Dosed in corn oil.
Method	:	Standing Operating Procedure No. 25, Teratology Study in Rats, July 1981, Toxicology Division, U.S. Army Environmental Hygiene Agency.
Method detail	:	Doses were set based on results of a pilot study. There were at least 33 positively mated females in each dose group. Females were sacrificed on day 20 of gestation. Each uterus was exposed and counts were made of corpora lutea, implantation sites, resorptions, and fetuses. Fetuses were preserved and examined for either skeletal (even-numbered fetuses) or soft tissue (odd numbered fetuses) malformations.
Result	:	Oral administration of zinc naphthenate to rats during the major period of organogenesis did not result in teratogenic effects. Transient maternal toxicity was confined to the highest dosage group (938 mg/kg/day) and consisted of lethargy and lower body weight gain. Maternal treatment at that dosage level also produced a higher incident of resorptions and lower average fetal body weights. Dams receiving zinc naphthenate at either 94 or 188 mg/kg/day were not adversely affected, nor were their developing fetuses. Compared to controls, there was an increase in the incidence of variants (minor morphological deviations) in all treatment groups; however, there was not a dose-response for this effect. It was concluded that zinc naphthenate is not teratogenic and does not cause developmental toxicity at doses that are not maternally toxic.
Remark	:	**Supporting data for dissociation products:** **Metal:** Second-generation mice (from mothers fed zinc carbonate) exposed to high doses of zinc throughout the gestation, lactation, and postweaning period had elevated levels of zinc in their bones, decreased blood copper

levels, lowered hematocrit values and reduced body weights. The offspring of pregnant rats fed zinc carbonate (500 mg Zn/kg) did not demonstrate any increase in the incidence of malformations. (WHO, 2001, Environmental Health Criteria 221, Zinc). Several developmental toxicity studies were conducted with zinc sulfate on mice, rats, hamsters and rabbits, in general accordance with OECD Guideline 414; however, the form of the zinc sulfate was not specified. Depending upon the form that was used, the calculated NOAEL values ranged from 6.8 mg Zn/kg bw for the mouse to 35.2 mg Zn/kg bw for the hamster. (Risk Assessment for Zinc Metal, 2001, draft).

Reliability : [1] Reliable without restriction. Comparable to guideline study.

Reference : Angerhofer, R.A., M.W. Michie, M.P. Barlow, and P.A. Beall. 1991 Phase 4, Toxicological Study No. 75-51-0497-91, Assessment of the developmental toxicity of zinc naphthenate in rats, June 1985 – July 1988. U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD. NTIS No. ADA235308.

Type : Oral administration

Guideline/method : FIFRA 83-3

Species : Rat

Strain : Sprague-Dawley Crl:CDBR

Sex : Female

Route of admin. : Oral

Exposure period : Day 6 through 15 of gestation

Frequency of treatment : Daily

Duration of test : Mating until day 20 of gestation

Doses : 50, 250, and 500 mg/kg/day

Control group : Yes (received 10 mL/kg/day of corn oil)

NOAEL maternal tox. : 250 mg/kg/day (excluding marginal clinical signs)

NOAEL teratogen. : 500 mg/kg/day

Other : LOAEL was 500 mg/kg/day for maternal toxicity (based on clinical signs and slightly reduced food consumption)

Other : LOAEL for fetuses was above the highest dose tested

Other :

Year : 1990

GLP : Yes

Test substance : Technical grade zinc naphthenate (purity = 98.9%; 14.3% Zn).

Method : Oral gavage

Method detail : Doses were set based on results of a range-finding study. The test substance was dissolved in corn oil and administered by gastric gavage at a dose volume of 10 ml/kg. There were 25 positively mated females in each dose group. Females were sacrificed on day 20 of gestation for a scheduled Cesarean section. The uteri and ovaries were examined and the location and numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Fetuses were weighed, sexed, and examined for external, skeletal and soft tissue malformations and developmental variations.

Result : Maternal survival was not adversely affects in the study and no indication of maternal toxicity was apparent at a dose level of 50 mg/kg/day. Clinical signs of toxicity observed in the high dose females included anogenital and/or urogenital staining, staining around the mouth, and salivation. Some of the same clinical signs were also seen in females at the mid-dose level, although the incidence was greatly reduced. No adverse effects were apparent on body weight data or gravid uterine weight data although food consumption was slightly reduced in the high dose group. Intrauterine growth and survival were not adversely affected at any of the treatment levels. The nature and frequency of fetal malformations and developmental

levels. The nature and frequency of fetal malformations and developmental variations expressed appeared to be spontaneous in origin.

Remark : Results are highly consistent with the developmental toxicity study conducted on zinc naphthenate by the U.S. Army Environmental Hygiene Agency (see above).

Reliability : [1] Reliable without restriction. Comparable to guideline study.

Reference : Nemec, M.D. 1990. A developmental toxicity study of zinc naphthenate in rats. WIL Research Laboratories, Inc. Lab Study No. WIL-153004.

5.8.3 TOXICITY TO REPRODUCTION

Type : Two generation, oral administration

Guideline/method :

In vitro/in vivo : In vivo

Species : Rat

Strain : Sprague-Dawley

Sex : Male and female

Route of admin. : Diet

Exposure period : Two generations

Frequency of treatment : Continuous in diet

Duration of test : Through weaning of second (F2) generation of offspring

Doses : 500, 1000, or 5000 ppm in diet

Control group : Yes

Year : 1991

GLP : Yes

Test substance : Zinc naphthenate, technical, containing 13.7% zinc. Dosed in corn oil.

Method : Standing Operating Procedure, Reproduction Study in Rats, August 1986 revision, Toxicology Division, U.S. Army Environmental Hygiene Agency.

Method detail : Rats were fed zinc naphthenate for 10 weeks prior to mating of the parental (P) generation. Feeding of the treated diet was continued during mating, gestation, and lactation for both the P and F1 generations. Body weights and feed consumption were measured three times per week during the exposure period. Animals were checked daily for toxic signs. After sacrifice, animals were examined grossly and target organ tissues removed for histopathologic examination. Individual body weights, abnormalities, mortalities, and total litter weights for F1 pups were noted on days 0, 4, 7, 14, and 21 post partum.

Results : The continuous diets of zinc naphthenate employed in the study produced no adverse effects on reproductive function of rats over two generations. Rats fed a diet of 5,000 ppm experienced a significant weight loss (or reduced weight gain), but this effect had no subsequent effect on mating or viability of offspring over two generations. It is concluded that zinc naphthenate does not produce adverse effects on reproduction at dietary levels that are not maternally or paternally toxic. The NOAEL for all endpoints in this study was 1,000 ppm in the diet.

Remark : **Supporting data for related salts:**
Results of the oral reproduction study are consistent with a one generation dermal reproduction study in male rabbits conducted on SAP 011, an overbased calcium naphthenate in mineral oil. A group of 12 male New Zealand White rabbits was dermally exposed to 2 ml of undiluted SAP 011 for 6 hours daily for 5 days each week over a 10-week period. Following the exposure period, each male rabbit was mated with two untreated female rabbits. Males were subsequently necropsied and their reproductive tracts examined macroscopically and microscopically. Female rabbits were necropsied on day 29 of gestation and examined for reproductive

necropsied on day 29 of gestation and examined for reproductive parameters. Study results showed no adverse effects on reproductive performance due to male exposure. There were no adverse signs of toxicity either systemically or at the site of application in treated males, as well as no pathological findings of the reproductive tract that could be related to SAP 011 exposure. Reference: Dix, K.M. and S.L. Cassidy. 1983. Toxicity studies on oil additives: one generation reproduction study in male rabbits repeatedly treated dermally with SAP 0111 for 10 weeks. External Report SBER.84.002. Shell Research Ltd. (NTIS No. OTS0507494).

Supporting data for dissociation products:
Metal: Rats fed zinc chloride daily over an 8 week period demonstrated altered sperm chromatin structure with a LOAEL of 25 mg Zn/kg/d. The LOAEL for serious reproductive effects in female rats was 200 and 250 mg Zn/kg/d from exposure to zinc sulfate and zinc carbonate, respectively, in the diet. (ATSDR, 1994, Toxicological Profile for Zinc).

Reliability : [1} Reliable without restriction. Comparable to guideline study.

Reference : Michie, M.W., Angerhofer, R.A., M.P. Barlow, and P.A. Beall. 1991 Phase 5, Effects of ingestion of zinc naphthenate on reproductive function of rats, Toxicological Study No. 75-51-0497-91. U.S. Army Environmental Hygiene Agency, Aberdeen Proving Ground, MD. NTIS No. ADA235224.

15.0 OTHER INFORMATION

15.1 Carcinogenicity

No adequate experimental evidence has been found to indicate that zinc salts administered orally or parenterally are tumorigenic. (WHO, 2001, Environmental Health Criteria 221, Zinc).

6.2 Skin sensitization

Zinc sulfate is not a skin sensitizer in animals. (Risk Assessment for Zinc Metal, 2001, draft).

ROBUST SUMMARIES

For

Copper Naphthenate

Copper Naphthenate is a FIFRA Chemical and not sponsored under the HPV Challenge Program. Robust summaries are provided here in support of the existing data for metal carboxylates cobalt and zinc naphthenate.

Prepared by

MorningStar Consulting, Inc.

on behalf of

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

DECEMBER 20, 2002

1.0 SUBSTANCE INFORMATION

Generic Name	:	Copper naphthenate
Chemical Name	:	Naphthenic acids, copper salts
CAS Registry No.	:	1338-02-9
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	Variable
Molecular Weight	:	
Synonyms and Tradenames	:	
References	:	

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value : at °C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value : hPa at °C
Decomposition :
Year :

GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.7 FLASH POINT

Type :
Guideline/method :
Value : °C
Year :

GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Halflife (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.2 STABILITY IN WATER

Type : biotic
Guideline/method :
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Degradation : after at pH and °C
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.2.1 MONITORING DATA

Type of measurement : concentration at contaminated site

Media : ground water
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %
%
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :

Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	Static
Guideline/method	:	FIFRA 72-1
Species	:	Rainbow trout (*Oncorhynchus mykiss*)
Exposure period	:	96 h
NOEC	:	<0.13 mg/L
LC0	:	
LC50	:	0.18 mg/L (95% C.I. = 0.11 – 0.23 mg/L)
LC100	:	0.51 mg/L
Other	:	Slope of dose response curve = 5.6722
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	Yes
Year	:	1992
GLP	:	Yes
Test substance	:	Copper naphthenate, purity = 95.6%
Method	:	Nominal test concentrations: 0.13, 0.23, 0.36, 0.60, and 1.0 mg/L.
Method detail	:	Stock solution was made in acetone. Maximum concentration of acetone in any test vessel was 0.5 ml/L. Temperature = 12 – 13 °C. pH = 7.1 - 7.5
Result	:	Mean measured concentrations averaged 90% of the nominal concentrations.
Remark	:	A similar acute test on the bluegill, *Lepomis macrochirus*, produced an 96-hr LC50 of 3.2 mg/L and an LOEC of 1.6 mg/L. (Collins, M.K. 1992. Copper naphthenate – acute toxicity to bluegill sunfish (Lepomis macrochirus) under static renewal conditions. Springborn Laboratories, Inc. SLI Report 92-3-4147.
Reliability	:	1 (reliable without restriction)
Reference	:	Collins, M.K. 1992. Copper naphthenate – acute toxicity to rainbow trout (*Onchorhynchus mykiss*) under static conditions. Springborn Laboratories, Inc. SLI Report 92-1-4086.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	Static
Guideline/method	:	FIFRA 72-2
Species	:	*Daphnia magna*
Exposure period	:	48 hr
NOEC	:	0.12 mg/L
EC0	:	0.12 mg/L
EC50	:	0.34 mg/L (95% C.I. = 0.29 - 0.39 mg/L)
EC100	:	0.86 mg/L
Other	:	Slope of dose-response curve = 7.233
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	Yes
Year	:	1992
GLP	:	Yes
Test substance	:	Copper naphthenate, purity = 95.6%
Method	:	Nominal test concentrations: 0.13, 0.22, 0.36, 0.60, and 1.0 mg/L.
Method detail	:	Stock solution was made in acetone. Maximum concentration of acetone in any test vessel was 0.5 ml/L. Temperature = 19 – 21 °C. pH = 8.2 – 8.4
Result	:	Mean measured concentrations averaged 89% of the nominal

		concentrations.
Remark	:	
Reliability	:	1 (reliable without restriction)
Reference	:	Collins, M.K. 1992. Copper naphthenate – acute toxicity to daphnids (*Daphnia magna*) under static conditions. Springborn Laboratories, Inc. SLI Report 92-2-4096.

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:
Guideline/method	:
Species	:
Endpoint	:
Exposure period	:
NOEC	:
LOEC	:
EC0	:
EC10	:
EC50	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	Acute single dose
Guideline/Method	:	FIFRA 81-1
Species	:	Rat
Strain	:	Sprague-Dawley
Sex	:	Both male and female
Number of animals	:	10 per dose level (5 male, 5 female)
Vehicle	:	Corn oil
Doses	:	1,000; 3,000; 5,000; 7,000; 9,000; and 10,000 mg/kg
LD50	:	5,800 mg/kg (95% C.I. interval = 4,580 – 7,350 mg/kg)
Year	:	1987
GLP	:	No
Test substance	:	8% copper naphthenate (M-Gard S520)
Method	:	
Method detail	:	
Result	:	All mortalities, except for one, occurred within the first 4 days after dosing. Gross pathology of dead animals showed hemorrhagic lungs, darkened livers, slightly dark to dark kidneys and spleens, and hemorrhagic stomachs

livers, slightly dark to dark kidneys and spleens, and hemorrhagic stomachs and intestines with discolored fluids.

Remark : The acute LD50 for a related compound described as 2% copper naphthenate, solvent was greater than 5,000 mg/kg. One of 10 dosed animals died during the study. Reference: Applied biological Sciences Laboratory, 1985. Laboratory Study No. 2585.

Reliability : 2 (reliable with restrictions). Test substance purity and composition is unknown and does not necessarily represent neat copper naphthenate.

Reference : Lacap, L.F. and G.J. Letizia. 1987. Report on acute oral LD50 in rats using 8% copper naphthenate, F-19273 (M-Gard S520). Wells Laboratories Inc., Study No. L-1527.

5.1.2 ACUTE INHALATION TOXICITY

Type : Acute LC50
Guideline/method : FIFRA 81-3
Species : Rat
Strain : Crl:CD(SD)BR
Sex : Male and female
Number of animals : 5 per sex per treatment
Vehicle : Xylene
Doses : 2.966 mg/L
Exposure time : 4 hr
LC50 : >2.966 mg/L (measured)
Year : 1990
GLP : Yes
Test substance : Copper naphthenate
Method :
Method detail : One group of 10 rats (5 of each sex) was exposed to copper naphthenate at a single chamber concentration of 2.966 mg/L by inhalation (whole-body) over a period of 4 hours. The nominal concentration was 7.524 mg/L. Exposure was followed by an observation period of 14 days. Chamber airflow was 20 L/Min. The mean mass aerodynamic diameter of the particles in the atmosphere was 1.71 µm.
Result : There were no deaths in the study, although treatment-related clinical signs (piloerection, salivation, nasal secretion, lethargy, respiratory distress) were observed on the day of exposure. Body weight gain was slightly reduced in the treated animals. There were no treatment-related macroscopic abnormalities.
Remark :
Reliability : 1 Reliable without restriction.
Reference : Collins, C.J. 1990. Copper naphthenate acute inhalation toxicity study – LC50 rats (4 hour exposure). Hazelton UK. Lab Study No. 6320-769/1.

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :

Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type	:	90-Day dermal toxicity
Guideline/method	:	FIFRA 82-3
Species	:	Rat
Strain	:	Crl:CD®BR
Sex	:	Male and female
Number of animals	:	10 per sex per treatment group
Route of admin.	:	Dermal
Exposure period	:	6 hours per day for 13 weeks
Frequency of treatment	:	Once per day; 5 days per week
Post exposure period	:	None
Doses	:	100, 300, or 1000 mg/kg/day
Control group	:	Yes
NOAEL	:	1000 mg/kg/day (for systemic toxicity)
LOAEL	:	Not determined for systemic toxicity
Other	:	
Year	:	1990
GLP	:	Yes
Test substance	:	Copper naphthenate (9.5% copper; purity not specified)
Method	:	
Method detail	:	Test substance was dissolved in light mineral oil at a concentration of 80% by weight and administered onto the clipped intact dorsal skin of each animal. After application, each test site was wrapped with a gauze binder and the dressing secured with Deriform® tape. At the end of a 6-hour exposure period, the dressings were removed and the test sites were wiped with disposable paper towels moistened with mineral oil. The concurrent control group received the vehicle (mineral oil) on a comparable regimen at a dose volume equal to the amount of vehicle received by the highest dose group.
Result	:	Erythema and edema were observed in all treated groups during the study. The frequency and severity of effects were dose-related. In general, the severity of both findings increased during the initial four weeks of dosing, then decreased. Histopathologic evaluation of the application sites revealed a low incidence of dermal hyperplasia, supportive inflammation and hyperkeratosis in rats at the 300 and 1000 mg/kg/day dose levels. No effects on survival, clinical observations, and other parameters used to evaluate systemic toxicity were apparent at any dose level during the study, thus a dose level of 1000 mg/kg/day was the NOAEL for systemic toxicity.
Remark	:	
Reliability	:	(2) Reliable with restrictions. Purity of test material was not specified.
Reference	:	Tomkins, E.C. 1990. 90-Day dermal study in rabbits with copper naphthenate. WIL Research Laboratories. Lab Study No. WIL-153012.

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Mutagenicity
Guideline/method	:	TSCA 40 CFR Part 798.5265
System of testing	:	Ames bacterial/microsomal plate incorporation
Species	:	*Salmonella typhimurium*
Strain	:	TA98, TA100, TA1535, TA1537, TA1538
Test concentrations	:	0.05 to 0.5 mg/plate
Cytotoxic concentr.	:	1.0 mg/plate
Metabolic activation	:	Yes, 0.5 ml of rat liver S9 fraction

Year	:	1988
GLP	:	Yes
Test substance	:	Copper naphthenate (purity and composition unknown)
Method	:	Ames Salmonella Mutagenesis Assay
Method detail	:	Test substance was dissolved in DMSO. Assay was run in triplicate. A negative and four positive controls were included.
Result	:	The test substance did not cause a positive increase in the number of histidine revertant colonies and exhibited similar results to the vehicle control, therefore, it is considered non-mutagenic according to the procedure employed.
Remark	:	
Reliability	:	2 Reliable with restrictions. Test substance purity and composition is unknown and does not necessarily represent neat copper naphthenate.
Reference	:	Desai, L.S., A. Raghupathy, and N. DiGiulio. 1988. Ames bacterial/ microsomal plate incorporation assay. Toxikon Corp., Project No. 88G-0096.

Type	:	Cytogenetics assay (chromosome aberrations)
Guideline/method	:	FIFRA 84-2
System of testing	:	Chinese hamster ovary (CHO) cells
Species	:	Hamster
Strain	:	Chinese
Test concentrations	:	Up to 200 µg/ml in activated system; up to 160 µg/ml in unactivated system
Cytotoxic concentr.	:	Approx. 80 µg/ml without activation; Approx. 60 µg/ml with activation
Metabolic activation	:	Yes, with Aroclor induced S-9 fraction from male Sprague-Dawley rats
Year	:	1990
GLP	:	Yes
Test substance	:	Copper naphthenate (purity and copper composition unknown)
Method	:	
Method detail	:	Acetone was used to dissolve the test substance and as a solvent control. Triethylenemelamine and cyclophosphamide were used as positive controls. Whenever possible, a minimum of 100 metaphase spreads (50 per duplicate flask) were examined and scored for chromatid-type and chromosome-type aberrations.
Result	:	No significant increase in chromosome aberrations was observed in the either the activated or the nonactivated test systems. A marginal increase in the number of aberrations was seen at a concentration of 60 µg/ml in the activated system, but in subsequent testing this was not found to be reproducible at similar and higher concentrations.
Remark	:	
Reliability	:	2 Reliable with restrictions. Test substance purity and composition is unknown.
Reference	:	Putman, D.L and M.J. Morris. 1990. chromosome aberrations in Chinese hamster ovary (CHO) cells – copper naphthenate. Microbiological Associates, Inc. Lab Study No. T9037.337.

Type	:	L5178Y TK+/- Mouse lymphoma mutagenesis
Guideline/method	:	FIFRA 84-2
System of testing	:	Mouse lymphoma assay
Species	:	Mouse
Strain	:	L5178Y TK+/-

Test concentrations	:	Initial assay: 4.2 – 56 µg/ml (nonactivated); 3.2 - 42 µg/ml (S-9 activated) Confirmatory assay: 7.5 – 36 µg/ml (nonactivated); 7.5 - 36 µg/ml (activated)
Cytotoxic concentr.	:	100 µg/ml (100% toxicity)
Metabolic activation	:	Yes, with Aroclor induced S-9 fraction
Year	:	1990
GLP	:	Yes
Test substance	:	Copper naphthenate (purity and copper composition not specified)
Method	:	Clive and Spector, 1975 (Mutation Res. 31:17-29)
Method detail	:	Acetone was used as the solvent for preparing dilutions of the test substance. Both initial assay and a confirmatory assay were conducted with and without metabolic activation.
Result	:	In both the initial and the confirmatory assays, copper naphthenate appeared to be more cytotoxic in the presence of metabolic activation. Copper naphthenate did not induce significant mutagenesis in the absence of activation, but produced a dose-dependent response in mutagenesis in the presence of metabolic activation. Positive results with activation were produced in both the initial assay and the confirmatory assay. Colony sizing data for both assays with activation suggested an increase in the relative proportion of small colonies.
Remark	:	
Reliability	:	2 Reliable with restrictions. Test substance purity and composition is unknown.
Reference	:	Harbell, J.W. 1990. L5178Y TK+/- mouse lymphoma mutagenesis assay with confirmation – copper naphthenate. Microbiological Associates, Inc. Lab Study No. T9037.701.

Type	:	Unscheduled DNA synthesis
Guideline/method	:	FIFRA 84-2; OECD 482
System of testing	:	Rat primary hepatocyte cultures
Species	:	Rat
Strain	:	Sprague-Dawley
Test concentrations	:	0.5 to 50 µg/ml
Cytotoxic concentr.	:	15 µg/ml and above
Metabolic activation	:	No
Year	:	1989
GLP	:	Yes
Test substance	:	Copper naphthenate (purity and copper composition unknown)
Method	:	Williams, G. M. 1977. Carcinogen-induced DNA repair in primary rat liver cell cultures, a possible screen for chemical-carcinogens. Canc. Lett. 1:231-237.
Method detail	:	Test substance was dissolved in acetone. Unscheduled DNA synthesis was assessed on the basis of ^{3}H-thymidine incorporation in the cell.
Result	:	In the range-finding test, the test substance was observed to form precipitates in the culture medium at concentrations of 135 µg/ml and higher. Cells exposed to 15 µg/ml exhibited signs of toxicity (some cells had small and irregularly shaped nuclei). Only nuclei with acceptable morphology were evaluated for UDS. The test article did not cause a significant increase in the mean net nuclear grain counts (i.e., an increase of at least 5 counts over solvent control) at concentrations that were not cytotoxic (0.15 to 5.0 µg/ml). Therefore, the test article gave negative results in the study. All criteria for a valid test were met.
Remark	:	

Reliability	:	2 Reliable with restrictions. Test substance purity and composition is unknown.
Reference	:	Curren, R.D. 1989. Unscheduled DNA synthesis in rat primary hepatocytes – copper naphthenate. Microbiological Associates, Inc. Lab Study No. T9037.380.

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Doses	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	Teratology / developmental toxicity
Guideline/method	:	FIFRA 83-3
Species	:	Rat
Strain	:	Sprague-Dawley Crl:CD®BR
Sex	:	Female
Route of admin.	:	Gastric intubation
Exposure period	:	Day 6 through 15 of gestation
Frequency of treatment	:	Daily
Duration of test	:	Mating until day 20 of gestation
Doses	:	30, 100, and 300 mg/kg/day
Control group	:	Yes (received 10 mL/kg/day of corn oil)
NOAEL maternal tox.	:	30 mg/kg/day
NOAEL teratogen.	:	100 mg/kg/day
Other	:	LOAEL was 100 mg/kg/day for maternal toxicity (based on clinical signs, reduced food consumption, and reduced body weight)
Other	:	LOAEL for developmental toxicity was 300 mg/kg/day based on a slight increase in postimplantation loss
Other	:	
Year	:	1990
GLP	:	Yes
Test substance	:	Copper naphthenate (9.5% copper; purity not specified)
Method	:	Oral gavage
Method detail	:	Doses were set based on results of a range-finding study. The test substance was dissolved in corn oil and administered by gastric gavage at a dose volume of 10 ml/kg. There were 25 positively mated females in each dose group. Females were sacrificed on day 20 of gestation for a

dose group. Females were sacrificed on day 20 of gestation for a scheduled Cesarean section. The uteri and ovaries were examined and the location and numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Fetuses were weighed, sexed, and examined for external, skeletal and soft tissue malformations and developmental variations.

Result : Evidence of maternal toxicity was found in the 100 and 300 mg/kg/day dose groups, including clinical signs, reduced food consumption, and reduced body weight. Postimplantation loss was slightly increased in the 300 mg/kg/day group due to one female with an entire litter resorption; however, this was the only developmental effect in the study that was considered to be potentially treatment-related.

Remark :

Reliability : 2 Reliable with restrictions. Test substance purity was not specified

Reference : Nemec, M.D. 1990. A developmental toxicity study of copper naphthenate in rats. WIL Research Laboratories, Inc. Lab Study No. WIL-153002.

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

16.0 OTHER INFORMATION

16.1 CARCINOGENICITY

1.0 SUBSTANCE INFORMATION

Generic Name	:	
Chemical Name	:	Neodecanoic acid, cobalt salt
CAS Registry No.	:	27253-31-2
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$Co(C_{10}H_{19}O_2)_2$
Molecular Weight	:	401.46
Synonyms and Tradenames	:	Cobalt neodecanote; 2,2-dimethyloctanoic acid, cobalt salt
References	:	

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	426 - 517 °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	Material Safety Data Sheet for 14% Cobalt Neodecanoate, OMG Americas, Inc.

2.3 DENSITY

Type	:	Specific gravity
Guideline/method	:	
Value	:	1.07 at 25°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	Material Safety Data Sheet for 14% Cobalt Neodecanoate, OMG Americas, Inc.

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	hPa at °C

Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow :
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value :
pH value :
concentration :
Temperature effects :
Examine different pol. :
PKa :
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.7 FLASH POINT

Type :
Guideline/method :

Value	:	230 °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	Material Safety Data Sheet for 14% Cobalt Neodecanoate, OMG Americas, Inc.

3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Halflife (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.2 DISSOCIATION

Type : Dissociation constant determination
Guideline/method : OECD 112
pka : 6.52 at 20°C
Year : 2002
GLP : Yes
Test substance : Cobalt neodecanoate, 14%, received from OMG. Purple semi-solid, purity of 14.2% cobalt.
Approximate water solubility : 2.9 mg/L as determined by Inductively Coupled Plasma Atomic Emission Spectrometry in preliminary study
Method : OECD Guideline 112, Dissociation Constants in Water
Method detail : Three replicate samples of neodecanoic acid, cobalt salt were prepared at a nominal concentration of 1.5 mg/L by fortification of 100 mL of degassed water (ASTM Type II) with a 1.0 mg/mL stock solution of the test substance in tetrahydrofuran. Each sample was titrated against 0.0025 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result : Mean (N = 3) pKa value was 6.52 (SD = 0.00351) at 20°C
Remark : The results indicate that dissociation of the test substance will occur at

environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of neodecanoic acid, cobalt salts, Wildlife International, Ltd. Study No. 534C-119, conducted for the Metals Carboxylate Coalition.

3.2.1 MONITORING DATA

Type of measurement : concentration at contaminated site
Media : ground water
Concentration : mg/l
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %

%

Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Data for dissociation products:**
Acid: Neodecanoic acid is not readily biodegradable. Approximately 11% was degraded over 28 days in a manometric respirometry test (OECD 301F). Exxon Biomedical Sciences, 1996. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
LC0 :
LC50 :
LC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: For neodecanoic acid, the 96-h LC50 for the bluegill (*Lepomis macrochirus*) has been reported as 60 mg/L under static conditions. Reference 9 in the year 2000 IUCLID dataset for neodecanoic acid. For the goldfish (*Carassius auratus*), the 96-h LC50 for neodecanoic acid has been reported as 56 mg/L under static conditions. Reference 6 in the year 2000 IUCLID dataset for neodecanoic acid. For the sheepshead minnow (*Cyprinodon variegatus*), the 96-h LC50 for neodecanoic acid has been reported as 181 mg/L under static conditions. Reference 7 in the year 2000 IUCLID dataset for neodecanoic acid. For the rainbow trout (*Oncorhynchus mykiss*), the 96-h LC50 for neodecanoic acid is 37.2 mg/L. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.
Metal: For cobalt chloride, the 96-h LC50 was 333 mg Co/L for *Cyprinus carpio* and 1,406 mg Co/L for *Onchorynchus mykiss* (ECOTOX data base).
Reliability :
Reference :

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
EC0 :
EC50 :
EC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :

GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: For neodecanoic acid, the 48-h EC50 for *Daphnia magna* has been reported as 47.1 mg/L. EG&G Bionomics, 1977. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co. For the copepod, *Acartia tonsa*, the 96-h LC50 for neodecanoic acid has been reported as 25 mg/L. Reference 14 in the year 2000 IUCLID dataset for neodecanoic acid.

Metal: For cobalt chloride, the reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base).
Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: For cobalt chloride, the 96-h EC50 for *Chorella vulgaris* was 0.522 mg Co/L (ECOTOX data base).
Reliability :
Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo :
Type :
Guideline/method :
Species :
Number of animals :
Males :
Females :
Doses :
Males :
Females :
Vehicle :
Route of administration :
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behavior :
Deg. product :
Deg. products CAS# :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. Clin. Tox. 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :

Guideline/Method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The acute oral LD50 of neodecanoic acid in the rat has been reported as 2700 – 3450 mg/kg. Reference 16 in the year 2000 IUCLID dataset for neodecanoic acid. The acute LD50 of 2,2-dimethyloctanoic acid (neodecanoic acid) in the rat is 2000 mg/kg. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.
Metal: Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg CoCl2/kg bw (equivalent to 19.1 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 55.4 to 72.5 mg Co/kg bw) (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 55.4 mg/kg bw when expressed as cobalt (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The acute inhalation LC50 for neodecanoic acid in the rat has been reported as >73 ppm for an exposure period of 6 hours. Reference 17 in the year 2000 IUCLID dataset for neodecanoic acid.

the year 2000 IUCLID dataset for neodecanoic acid.

The acute inhalation LC50 for 2,2-dimethyloctanoic acid (neodecanoic acid) in rats and mice has been reported as >3.0 mg/L for a single exposure of 6 hours. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

The acute inhalation LC50 for 2,2-dimethyloctanoic acid (neodecanoic acid) in rats, mice andhguinea pigs has been reported as >511 mg/M^3 for a single exposure of 6 hours. Bio/dynamics, Inc., 1982. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociationproducts:**
Acid: The acute dermal LD50 for neodecanoic acid in the rat has been reported as >3640 mg/kg. Reference 20 in the year 2000 IUCLID dataset for neodecanoic acid. The acute dermal LD50 in the rabbit is >3160 mg/kg. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :

Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Neodecanoic acid was found to be non-irritating to skin when tested on the rabbit according to OECD Guideline 404. Reference 22 in the year 2000 IUCLID dataset for neodecanoic acid.
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Neodecanoic acid was found to cause eye irritation when tested on the rabbit using the Draize test. Reference 23 in the year 2000 IUCLID dataset for neodecanoic acid.
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :

LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: When administered to rats in their feed for 3 months, the NOAEL for a 30% preparation of neodecanoic acid was 500 ppm. The LOAEL was 1500 ppm and included changes in the renal tubules of both male and female rats. Morphological changes in the thyroid, including hyperplasia, were also seen in male rats at the feeding level of 1500 ppm. Reference 24 in the year 2000 IUCLID dataset for neodecanoic acid.

Beagle dogs receiving oral capsules containing neodecanoic acid daily for a period of 13 weeks ddi not show adverse effects at dosing levels of approximately 30 mg/kg and below. Effects on body weight and declines in hematocrit, hemoglobin and erythrocyte values were seen at doses of 94.8 mg/kg and above. Reference 27 in the year 2000 IUCLID dataset for neodecanoic acid.

Albino rabbits receiving 10 dermal applications of neodecanoic acid over a 14 day period showed no adverse effects at an exposure level 2.5 ml/kg. Reference 25 in the year 2000 IUCLID dataset for neodecanoic acid.

When administered dermally to rabbits (10 applications with a two-day rest between the 5th and 6th application), the NOAEL for systemic effects for 2,2-dimethyloctanoic acid (neodecanoic acid) was 2.28 mg/kg/d. Hazelton Laboratories, 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Metal: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.6 to 30.2 mg $CoCl_2$/kg/day (equivalent to 0.27 to 13.6 mg Co/kg/day) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in the rat at LOAELs ranging from 8.4 to 12.4 mg $CoCl_2$/kg/day with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :

Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Neodecanoic acid produced negative results in the Ames *Salmonella* assay (OECD Method 471) against four strains of bacteria when tested both with and without metabolic activation at levels up to 1500 µg/plate. Reference 28 in the year 2000 IUCLID dataset for neodecanoic acid.

Neodecanoic acid produced negative results in a cytogentic assay (OECD Method 473) with cultured human lymphocytes when tested both with and without metabolic activation at levels up to 800 µg/ml. Reference 29 in the year 2000 IUCLID dataset for neodecanoic acid.

Metal: Cobalt compounds with a valent state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be non-mutagenic in bacterial assays, but cobalt compounds with a valent state of III were weakly mutagenic (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (as cobalt chloride) (NOEL) (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :

Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
NOAEL maternal tox.	:	
NOAEL teratogen.	:	
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** See results in the following section for a multi-generation study with 2,2-dimethyloctanoic acid (neodecanoic acid). **Metal:** In a single developmental toxicity study (ATSDR Sept 2001 Draft) with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.8.3 TOXICITY TO REPRODUCTION

Type	:	
Guideline/method	:	
In vitro/in vivo	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	

Remark : **Supporting data for dissociation products:**
Acid: In an oral (feeding) multi-generation rat reproduction study with neodecanoic acid, no adverse effects were observed in the parental generation or the F_1 and F_2 generations at feeding levels up to 1500 ppm in the diet. Reproductive parameters were not affected and, at necropsy, there were no gross alterations that could be attributed to the test substance. Hazelton Labs, Inc., 1968. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Metal: Effects on reproduction in rats has been studied following oral exposure to cobalt chloride for 10 to 14 weeks. The resulting LOAELs ranged from 13.2 to 20 mg CoCl2/kg/day (or 5.9 to 9 mg Co/kg/day) (ATSDR Sept 2001 Draft). Similar results were observed in mice exposed to cobalt chloride for 10 to 13 weeks at exposures levels ranging from 23 to 58.9 mg CoCl2/kg/day (equivalent to 10.3 to 26.5 mg Co/kg/day). Additionally, reduced numbers of pregnant females and pups per litter, and reduced fertility were observed at the 58.9 mg CoCl2/kg/day exposure level (ATSDR Sept 2001 Draft).

Reliability :

Reference :

17.0 OTHER INFORMATION

17.1 CARCINOGENICITY

Supporting data for dissociation products:
Metal: The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). “No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt.” (ATSDR Sept 2001 Draft).

1.0 SUBSTANCE INFORMATION

Generic Name	:	
Chemical Name	:	Fatty Acids, C9-C13-Neo, Cobalt Salts
CAS Registry No.	:	68955-83-9
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	
Molecular Weight	:	
Synonyms and Tradenames	:	
References	:	

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.3 DENSITY

Type : Specific gravity
Guideline/method :
Value : 1.14 at 25°C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference Material Safety Data Sheet for Neo C9-C13 Acid, Cobalt Salts, OMG Americas, Inc.

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value : hPa at °C
Decomposition :

Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.7 FLASH POINT

Type :
Guideline/method :
Value : °C

Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 Dissociation

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	5.96 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Neo C9-13 Acid, Cobalt Salts, CAS no. 68955-83-9, received from OMG. Purple chunks, purity of 16.3% cobalt
Approximate water solubility	:	3.5 mg/L as determined by Inductively Coupled Plasma Atomic Emission Spectrometry in preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water
Method detail	:	Three replicate samples of fatty acid, C9-13-neo-, cobalt salts were prepared at a nominal concentration of 1.5 mg/L by fortification of 100 mL of degassed water (ASTM Type II) with a 1.0 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.0025 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKa value was 5.96 (SD = 0.0303) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at

environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of fatty acids, C9-13-neo-, cobalt salts, Wildlife International, Ltd. Study No. 534C-116, conducted for the Metal Carboxylates Coalition.

:

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration :
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :

Kinetic	:	%
		%
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Fatty acids, C9-C13, neo not readily biodegradable. Approximately 2.3% was degraded over 28 days in a manometric respirometry test (OECD 301F). Exxon Biomedical Sciences, 1996. See robust summary for fatty acids, C9-C13, neo in attached document prepared by ExxonMobil Chemical Co.
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
LC0 :
LC50 :
LC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Component Acid: For neodecanoic acid, the 96-h LC50 for the bluegill (*Lepomis macrochirus*) has been reported as 60 mg/L under static conditions. Reference 9 in the year 2000 IUCLID dataset for neodecanoic acid. For the goldfish (*Carassius auratus*), the 96-h LC50 for neodecanoic acid has been reported as 56 mg/L under static conditions. Reference 6 in the year 2000 IUCLID dataset for neodecanoic acid. For the sheepshead minnow (*Cyprinodon variegatus*), the 96-h LC50 for neodecanoic acid has been reported as 181 mg/L under static conditions. Reference 7 in the year 2000 IUCLID dataset for neodecanoic acid. For the rainbow trout (*Oncorhynchus mykiss*), the 96-h LC50 for neodecanoic acid is 37.2 mg/L. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.
Metal: For cobalt chloride, the 96-h LC50 was 333 mg Co/L for *Cyprinus carpio* and 1,406 mg Co/L for *Onchorynchus mykiss* (ECOTOX data base).
Reliability :
Reference :

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
EC0 :
EC50 :
EC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :

GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Component Acid:** For neodecanoic acid, the 48-h EC50 for *Daphnia magna* has been reported as 47.1 mg/L. EG&G Bionomics, 1977. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co. For the copepod, *Acartia tonsa*, the 96-h LC50 for neodecanoic acid has been reported as 25 mg/L. Reference 14 in the year 2000 IUCLID dataset for neodecanoic acid. **Metal:** For cobalt chloride, the reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base)
Reliability	:	
Reference	:	

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	
Guideline/method	:	
Species	:	
Endpoint	:	
Exposure period	:	
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Metal:** For cobalt chloride, the 96-h EC50 for *Chorella vulgaris* was 0.522 mg Co/L (ECOTOX data base).
Reliability	:	
Reference	:	

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo :
Type :
Guideline/method :
Species :
Number of animals :
Males :
Females :
Doses :
Males :
Females :
Vehicle :
Route of administration :
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behavior :
Deg. product :
Deg. products CAS# :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. Clin. Tox. 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :

Guideline/Method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Component Acid: The acute oral LD50 of neodecanoic acid in the rat has been reported as 2700 – 3450 mg/kg. Reference 16 in the year 2000 IUCLID dataset for neodecanoic acid. The acute LD50 of 2,2-dimethyloctanoic acid (neodecanoic acid) in the rat is 2000 mg/kg. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.
Metal: Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg CoCl2/kg bw (equivalent to 19.1 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 55.4 to 72.5 mg Co/kg bw) (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 55.4 mg/kg bw when expressed as cobalt (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Component acid: The acute inhalation LC50 for neodecanoic acid in the rat has been reported as >73 ppm for an exposure period of 6 hours.

rat has been reported as >73 ppm for an exposure period of 6 hours. Reference 17 in the year 2000 IUCLID dataset for neodecanoic acid.

The acute inhalation LC50 for 2,2-dimethyloctanoic acid (neodecanoic acid) in rats and mice has been reported as >3.0 mg/L for a single exposure of 6 hours. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

The acute inhalation LC50 for 2,2-dimethyloctanoic acid (neodecanoic acid) in rats, mice andhguinea pigs has been reported as >511 mg/M^3 for a single exposure of 6 hours. Bio/dynamics, Inc., 1982. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Metal: The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m3 as mixed cobalt oxides. (ASTDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was > 10 mg/L (IUCLID, 2000).

Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Component Acid: The acute dermal LD50 for neodecanoic acid in the rat has been reported as >3640 mg/kg. Reference 20 in the year 2000 IUCLID dataset for neodecanoic acid. The acute dermal LD50 in the rabbit is >3160 mg/kg. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.
Metal: Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :

Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Component Acid: Neodecanoic acid was found to be non-irritating to skin when tested on the rabbit according to OECD Guideline 404. Reference 22 in the year 2000 IUCLID dataset for neodecanoic acid.
Metal: Cobalt is reported to be irritating to the skin (IUCLID, 2000).
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Component Acid: Neodecanoic acid was found to cause eye irritation when tested on the rabbit using the Draize test. Reference 23 in the year 2000 IUCLID dataset for neodecanoic acid.
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :

Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Component Acid: When administered to rats in their feed for 3 months, the NOAEL for a 30% preparation of neodecanoic acid was 500 ppm. The LOAEL was 1500 ppm and included changes in the renal tubules of both male and female rats. Morphological changes in the thyroid, including hyperplasia, were also seen in male rats at the feeding level of 1500 ppm. Reference 24 in the year 2000 IUCLID dataset for neodecanoic acid.

Beagle dogs receiving oral capsules containing neodecanoic acid daily for a period of 13 weeks ddi not show adverse effects at dosing levels of approximately 30 mg/kg and below. Effects on body weight and declines in hematocrit, hemoglobin and erythrocyte values were seen at doses of 94.8 mg/kg and above. Reference 27 in the year 2000 IUCLID dataset for neodecanoic acid.

Albino rabbits receiving 10 dermal applications of neodecanoic acid over a 14 day period showed no adverse effects at an exposure level 2.5 ml/kg. Reference 25 in the year 2000 IUCLID dataset for neodecanoic acid.

When administered dermally to rabbits (10 applications with a two-day rest between the 5th and 6th application), the NOAEL for systemic effects for 2,2-dimethyloctanoic acid (neodecanoic acid) was 2.28 mg/kg/d. Hazelton Laboratories, 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Metal: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).

Reliability :

Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :
Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Component Acid: Neodecanoic acid produced negative results in the Ames *Salmonella* assay (OECD Method 471) against four strains of bacteria when tested both with and without metabolic activation at levels up to 1500 µg/plate. Reference 28 in the year 2000 IUCLID dataset for neodecanoic acid.

Neodecanoic acid produced negative results in a cytogentic assay (OECD Method 473) with cultured human lymphocytes when tested both with and without metabolic activation at levels up to 800 µg/ml. Reference 29 in the year 2000 IUCLID dataset for neodecanoic acid.

Metal: Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be non-mutagenic in bacterial assays, but cobalt compounds with a valence state of III were weakly mutagenic (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result : **Supporting data for dissociation products:**
Metal: Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells. Increased

salts, are reported to be clastogenic in mammalian cells. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (as cobalt chloride) (NOEL) (ATSDR Sept 2001 Draft).

Remark :
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociationproducts:**
Component Acid: See results in the following section for a multi-generation study with 2,2-dimethyloctanoic acid (neodecanoic acid).

Metal: In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type	:	
Guideline/method	:	
In vitro/in vivo	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Component Acid:** In an oral (feeding) multi-generation rat reproduction study with neodecanoic acid, no adverse effects were observed in the parental generation or the F_1 and F_2 generations at feeding levels up to 1500 ppm in the diet. Reproductive parameters were not affected and, at necropsy, there were no gross alterations that could be attributed to the test substance. Hazelton Labs, Inc., 1968. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co. **Metal:** Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

18.0 OTHER INFORMATION

18.1 CARCINOGENICITY

Supporting data for dissociation products:
Metal: The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). “No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt.” (ATSDR Sept 2001 Draft).

18.2 Skin Sensitization

Supporting data for dissociation products:

Component Acid: Neodecanoic acid was not found to be sensitizing when tested on the guinea pig using the Magnusson and Kligman maximization test. Reference 21 in the year 2000 IUCLID dataset for neodecanoic acid.

1.0 SUBSTANCE INFORMATION

Generic Name	:	
Chemical Name	:	Cobalt Borate Neodecanoate Complexes
CAS Registry No.	:	68457-13-6
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	
Molecular Weight	:	
Synonyms and Tradenames	:	Comend® A Pastillates Cobalt boro acylate
References	:	

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	°C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

2.3 DENSITY

Type	:	Specific gravity
Guideline/method	:	
Value	:	1.32 at 25°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	Material Safety Data Sheet for Comend® A Pastillates, Shepherd Chemical Co.

2.4 VAPOR PRESSURE

Type	:	
Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	

Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at 25°C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : at 25°C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.7 FLASH POINT

Type :
Guideline/method :
Value : >231 °C

Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	Material Safety Data Sheet for Comend® A Pastillates, Shepherd Chemical Co.

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 Dissociation

Type	:	Dissociation constant determination
Guideline/method		OECD 112
pKa		6.41 at 20°C
Year		2002
GLP		Yes
Test substance		Manobond C22.5; CAS no. 68457-13-6, received from OMG. Purple solid, purity of 22.5% cobalt.
Approximate water solubility		3.5 mg/L as determined by Inductively Coupled Plasma Atomic Emission Spectrometry in preliminary study
Method		OECD Guideline 112, Dissociation Constants in Water
Method detail		Three replicate samples of cobalt, borate neodecanoate were prepared at a nominal concentration of 1.5 mg/L by fortification of 100 mL of degassed water (ASTM Type II) with a 1.0 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.0025 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result		Mean (N = 3) pKa value was 6.41 (SD = 0.0411) at 20°C
Remark		The results indicate that dissociation of the test substance will occur at

	environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	[1] Reliable without restriction.
Reference	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of cobalt, borate neodecanoate complexes, Wildlife International, Ltd. Study No. 534C-118, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %
Control substance	:	
Kinetic	:	%

%

Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Data for dissociation products:**
Acid: Neodecanoic acid is not readily biodegradable. Approximately 11% was degraded over 28 days in a manometric respirometry test (OECD 301F). Exxon Biomedical Sciences, 1996. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
LC0 :
LC50 :
LC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: For neodecanoic acid, the 96-h LC50 for the bluegill (*Lepomis macrochirus*) has been reported as 60 mg/L under static conditions. Reference 9 in the year 2000 IUCLID dataset for neodecanoic acid. For the goldfish (*Carassius auratus*), the 96-h LC50 for neodecanoic acid has been reported as 56 mg/L under static conditions. Reference 6 in the year 2000 IUCLID dataset for neodecanoic acid. For the sheepshead minnow (*Cyprinodon variegatus*), the 96-h LC50 for neodecanoic acid has been reported as 181 mg/L under static conditions. Reference 7 in the year 2000 IUCLID dataset for neodecanoic acid. For the rainbow trout (*Oncorhynchus mykiss*), the 96-h LC50 for neodecanoic acid is 37.2 mg/L. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Metal: For cobalt chloride, the 96-h LC50 was 333 mg Co/L for *Cyprinus carpio* and 1,406 mg Co/L for *Onchorynchus mykiss* (ECOTOX data base).
Reliability :
Reference :

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
EC0 :
EC50 :
EC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :

Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: For neodecanoic acid, the 48-h EC50 for *Daphnia magna* has been reported as 47.1 mg/L. EG&G Bionomics, 1977. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co. For the copepod, *Acartia tonsa*, the 96-h LC50 for neodecanoic acid has been reported as 25 mg/L. Reference 14 in the year 2000 IUCLID dataset for neodecanoic acid.

Metal: For cobalt chloride, the reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base)
Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: For cobalt chloride, the 96-h EC50 for *Chorella vulgaris* was 0.522 mg Co/L (ECOTOX data base).
Reliability :
Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo :
Type :
Guideline/method :
Species :
Number of animals :
Males :
Females :
Doses :
Males :
Females :
Vehicle :
Route of administration :
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behavior :
Deg. product :
Deg. products CAS# :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. Clin. Tox. 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :

Guideline/Method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The acute oral LD50 of neodecanoic acid in the rat has been reported as 2700 – 3450 mg/kg. Reference 16 in the year 2000 IUCLID dataset for neodecanoic acid. The acute LD50 of 2,2-dimethyloctanoic acid (neodecanoic acid) in the rat is 2000 mg/kg. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Metal: Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg $CoCl_2$/kg bw (equivalent to 19.1 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 55.4 to 72.5 mg Co/kg bw) (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 55.4 mg/kg bw when expressed as cobalt (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The acute inhalation LC50 for neodecanoic acid in the rat has been reported as >73 ppm for an exposure period of 6 hours. Reference 17 in

reported as >73 ppm for an exposure period of 6 hours. Reference 17 in the year 2000 IUCLID dataset for neodecanoic acid.

The acute inhalation LC50 for 2,2-dimethyloctanoic acid (neodecanoic acid) in rats and mice has been reported as >3.0 mg/L for a single exposure of 6 hours. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

The acute inhalation LC50 for 2,2-dimethyloctanoic acid (neodecanoic acid) in rats, mice andhguinea pigs has been reported as >511 mg/M^3 for a single exposure of 6 hours. Bio/dynamics, Inc., 1982. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Metal: The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m3 as mixed cobalt oxides. (ASTDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was > 10 mg/L (IUCLID, 2000).

Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The acute dermal LD50 for neodecanoic acid in the rat has been reported as >3640 mg/kg. Reference 20 in the year 2000 IUCLID dataset for neodecanoic acid. The acute dermal LD50 in the rabbit is >3160 mg/kg. Esso Research and Engineering Co., 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.
Metal: Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :

Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Neodecanoic acid was found to be non-irritating to skin when tested on the rabbit according to OECD Guideline 404. Reference 22 in the year 2000 IUCLID dataset for neodecanoic acid.
Metal: Cobalt is reported to be irritating to the skin (IUCLID, 2000)
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Neodecanoic acid was found to cause eye irritation when tested on the rabbit using the Draize test. Reference 23 in the year 2000 IUCLID dataset for neodecanoic acid.
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :

Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: When administered to rats in their feed for 3 months, the NOAEL for a 30% preparation of neodecanoic acid was 500 ppm. The LOAEL was 1500 ppm and included changes in the renal tubules of both male and female rats. Morphological changes in the thyroid, including hyperplasia, were also seen in male rats at the feeding level of 1500 ppm. Reference 24 in the year 2000 IUCLID dataset for neodecanoic acid.

Beagle dogs receiving oral capsules containing neodecanoic acid daily for a period of 13 weeks ddi not show adverse effects at dosing levels of approximately 30 mg/kg and below. Effects on body weight and declines in hematocrit, hemoglobin and erythrocyte values were seen at doses of 94.8 mg/kg and above. Reference 27 in the year 2000 IUCLID dataset for neodecanoic acid.

Albino rabbits receiving 10 dermal applications of neodecanoic acid over a 14 day period showed no adverse effects at an exposure level 2.5 ml/kg. Reference 25 in the year 2000 IUCLID dataset for neodecanoic acid.

When administered dermally to rabbits (10 applications with a two-day rest between the 5th and 6th application), the NOAEL for systemic effects for 2,2-dimethyloctanoic acid (neodecanoic acid) was 2.28 mg/kg/d. Hazelton Laboratories, 1964. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co.

Metal: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).

Reliability :

Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :
Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Neodecanoic acid produced negative results in the Ames *Salmonella* assay (OECD Method 471) against four strains of bacteria when tested both with and without metabolic activation at levels up to 1500 µg/plate. (Reference 28 in the year 2000 IUCLID dataset for neodecanoic acid.)

Neodecanoic acid produced negative results in a cytogenetic assay (OECD Method 473) with cultured human lymphocytes when tested both with and without metabolic activation at levels up to 800 µg/ml. (Reference 29 in the year 2000 IUCLID dataset for neodecanoic acid).

Metal: Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be non-mutagenic in bacterial assays (ATSDR Sept 2001 Draft), but cobalt compounds with a valence state of III were weakly mutagenic.
Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result : **Supporting data for dissociation products:**
Metal: Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in a range of mammalian systems. For example, increased micronucleus formation was observed following i.p. injection of 12.4 and

micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (as cobalt chloride) (NOEL) (ATSDR Sept 2001 Draft).

Remark :
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result : **Supporting data for dissociation products:**
Acid: See results in the following section for a multi-generation study with 2,2-dimethyloctanoic acid (neodecanoic acid).

Metal: In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).

Remark :
Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :

Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation studies:** **Acid:** In an oral (feeding) multi-generation rat reproduction study with neodecanoic acid, no adverse effects were observed in the parental generation or the F_1 and F_2 generations at feeding levels up to 1500 ppm in the diet. Reproductive parameters were not affected and, at necropsy, there were no gross alterations that could be attributed to the test substance. Hazelton Labs, Inc., 1968. See robust summary for 2,2-dimethyloctanoic acid (C10) in attached document prepared by ExxonMobil Chemical Co. **Metal:** Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

19.0 OTHER INFORMATIO

19.1 Carcinogenicity

Supporting data for dissociation products:

Metal: The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). “No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt.” (ATSDR Sept 2001 Draft).

19.2 Skin Sensitization

Supporting data for dissociation products:
Acid: Neodecanoic acid was not found to be sensitizing when tested on the guinea pig using the Magnusson and Kligman maximization test. Reference 21 in the year 2000 IUCLID dataset for neodecanoic acid.

1.0 SUBSTANCE INFORMATION

Generic Name	:	
Chemical Name	:	Phenol, nonyl-, barium salt
CAS Registry No.	:	28987-17-9
Component CAS Nos.	:	
EINECS No.	:	249-359-7
Structural Formula	:	
Molecular Weight	:	
Synonyms and Tradenames	:	Barium nonylphenate Barium bis(nonylphenolate) Phenolate, nonyl-, barium
References	:	

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The melting point for nonylphenol has been reported to range from approximately –8 to 24.5 °C. (References 1, 6, and 7 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability :
Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The boiling point for nonylphenol has been reported to range from approximately 290 to 302 °C. The test material has also been reported to decompose before reaching its boiling point. (References 1, 6, 7, and 8 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value : at °C
Year :
GLP :
Test substance :

Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The density of nonylphenol has been reported as 0.93 g/cm^3 at 20 °C. (References 1, 6, and 8 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability :
Reference

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value : hPa at °C
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The vapor pressure of nonylphenol has been measured as approximately 0.0000455 hPa at 25 °C using EPA Guideline 40 CFR 795.1950. (Reference 7 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability : **Supporting data for dissociation products:**
Acid: The octanol/water partition coefficient (log Pow) of nonylphenol has been measured as 3.28 at 20 °C using OECD Guideline 107 and as >3.80 using an EPA guideline. (References 10 and 11 in the year 2000 IUCLID dataset for nonylphenol.)
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : at °C
pH value :

concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The water solubility of nonylphenol has been reported to range from 4.60 to 11.90 mg/L at 25 °C over the pH range of 5 to 9 using a TSCA guideline method. Solubility at pH 7 was 6.24 mg/L. (Reference 7 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability	:	
Reference	:	

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The flash point of nonylphenol has reported as 149 °C (open cup) and approximately 155 °C (closed cup). (References 1 and 8 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Half-life (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.2 DISSOCIATION

Type : Dissociation constant determination
Guideline/method : OECD 112
pKb : 8.34, 6.81, and 5.62 at 20°C
Year : 2002
GLP : Yes
Test substance : Therm-chek RC 225, lot number 52737, CAS no. 28987-17-9, eceived from Ferro Corporation. Viscous amber liquid, purity of 12.6% barium.
Approximate water solubility : 50 mg/L, as determined visually in preliminary study
Method : OECD Guideline 112, Dissociation Constants in Water
Method detail : Three replicate samples of phenol, nonyl-, barium salt were prepared at a nominal concentration of 25 mg/L by fortification of 100 mL degassed water (ASTM Type II) with a 10 mg/mL stock solution of the test substance in tetrahydrofuran. Each sample was titrated against 0.00025 N hydrochloric acid while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result : Mean (N = 3) pKb values were 8.34 (SD = 0.0352), 6.81 (SD = 0.0862) and 5.62 (SD = 0.0684) at 20°C

Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of phenol, nonyl-, barium salt, Wildlife International, Ltd. Study No. 534C-115, conducted for the Metals Carboxylate Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %
Control substance	:	

Kinetic	:	%
		%
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Nonylphenol has been reported to degrade 78% in 40 days under aerobic conditions in a modified Sturm test and 7% in 28 days under aerobic conditions in an ISO draft BOD test. (References 21 and 22 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The measured bioconcentration factor (BCF) for nonylphenol in the fathead minnow is 271 after a 20-day exposure at 22 °C. (Reference 23 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
LC0 :
LC50 :
LC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Acute LC50 values for nonylphenol range from 0.135 – 0.95 mg/L for several different freshwater and saltwater fish species. (References 24 to 28 in the year 2000 IUCLID dataset for nonylphenol.)

Metal: The acute toxicity of barium chloride has been tested in several fish species. Expressed in terms of the metal only, LC50 values ranged from 150 mg Ba/L for a 48-hr test with the brown trout (*Salmo trutta*) to 1,080 mg Ba/L for a 96-hr test with the western mosquitofish (*Gambusia affinis*). The 96-hr LC50 for the mummichog, *Fundulus heteroclitus*, was >1,000 mg Ba/L. (ECOTOX database)
Reliability :
Reference :

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
EC0 :
EC50 :
EC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :

Result :

Remark : **Supporting data for dissociation products:**
Acid: The *Daphnia magna* 48-h EC50 for nonylphenol is 0.14 mg/L. The 96-h EC50 for *Mysidopsis bahia* is 0.043 mg/L. (References 29 and 24 in the year 2000 IUCLID dataset for nonylphenol.)

Metal: The acute toxicity of barium chloride has been tested in several invertebrate species. Expressed in terms of the metal only, LC50 values ranged from 46 and 78 mg Ba/L for 96-hr tests with two crayfish, *Orconectes limosus* and *Austropotamobius palliipes pall*, to 238 mg Ba/L for a 96-hr test with the scud, *Gammarus pulex*. (ECOTOX database)

Reliability :

Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :

Remark : **Supporting data for dissociation products:**
Acid: 96-h EC50 values for nonylphenol are 0.41 and 0.027 mg/L for *Selenastrum carpicornutum* and *Skeletonema costatum*, respectively [Reference 24 (Ward and Boeri, 1990) in the year 2000 IUCLID dataset for nonylphenol.]. The 96-hr NOEC for the duckweed, *Lemna minor*, is 0.90 mg/L [Brooke et al., 1993. as cited in the European Union Risk Assessment Report for 4-Nonylphenol (Branched) and Nonylphenol. 2002. Final Report]. The 72-h EC50 values for biomass and growth rate for the green algae, *Scenedesmus subspicatus* were 0.056 and 0.323 mg/L, respectively [Kopf, 1997 as cited in the European Union Risk Assessment Report for 4-Nonylphenol (Branched) and Nonylphenol. 2002. Final Report].

Metal: The acute toxicity of barium chloride has been tested with the duckweed, *Lemna minor*. The 96-hr EC50 for growth for this species was 25 mg Ba/L. (ECOTOX database)

Reliability :

Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** Based largely on data from the structurally-related compound octylphenol, as well as limited data for nonylphenol, the absorption of nonylphenol from the gastrointestinal tract is initially rapid and probably extensive. There is evidence of extensive first pass metabolism when nonylphenol is absorbed from the G.I. tract. Because of this, bioavailability is believed to be limited to approximately 10 to 20% of the absorbed dose. Absorbed nonylphenol is widely distributed throughout the body, with the highest concentration in the fat. (Information from the European Union Risk Assessment Report for 4-Nonylphenol (Branched) and Nonylphenol. 2002. Final Report) **Metal:** A wide range of absorption efficiencies has been reported for barium in animal studies. The range of reported oral absorption factors for all animal studies is 0.7% to 85.0%; however, many of the studies determined absorption by a method that does not account for barium that is absorbed and then excreted in the feces, a route that is significant for barium. In general, the presence of food in the gastrointestinal tract appears to decrease barium absorption, and barium absorption appears to be higher in young animals compared to older ones. Studies with several different barium compounds indicate that soluble barium compounds (e.g., barium chloride) and/or barium compounds that yield a dissociated barium ion in the acid environment of the upper gastrointestinal tract (i.e., barium

chloride and barium sulfate) have similar absorption efficiencies. Once absorbed, the highest concentrations of barium are found in the bone (91% of total body burden). The feces is the primary route of excretion, accounting for 90% of more of the total eliminated. (Information from U.S. EPA, 1999, Toxicological Review of Barium and Compounds)

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :
Guideline/Method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The acute oral toxicity of nonylphenol has been measured in several studies with rats. The LD50 consistently fell within the range of 1,000 to 2,000 mg/kg bw, with one exception, a value of 580 mg/kg bw. (References 39 to 50 in the year 2000 IUCLID dataset for nonylphenol.)

Metal: The acute oral LD50 for barium chloride in the rat is 118 mg/kg (equivalent to 77.8 mg Ba/kg). (World Health Organization, 1990, Environmental Health Criteria 107 Barium)

Reliability :
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :

Remark :
Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The acute dermal toxicity (LD50) of nonylphenol to rabbits has been measured as greater than 2,000 mg/kg bw in two separate studies. (References 40 and 42 in the year 2000 IUCLID dataset for nonylphenol.)
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Nonylphenol has been reported as corrosive or severely irritating when applied to rabbit and rat skin in several different studies. (References 40, 42, 48, 49, and 52 to 59 in the year 2000 IUCLID dataset for nonylphenol.)

Metal: In rabbits, barium nitrate causes mild skin irritation after a 24-hr exposure. (World Health Organization, 1990, Environmental Health Criteria 107 Barium)

107 Barium)

Reliability :

Reference :

5.2.2 EYE IRRITATION

Type :

Guideline/method :

Species :

Strain :

Sex :

Concentration :

Dose :

Exposure time :

Number of animals :

Vehicle :

Classification :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark : **Supporting data for dissociation products:**
Acid: Nonylphenol has been reported as irritating or severely irritating when applied to rabbit eyes. (References 40 - 42, 48 - 50, 53, and 60 in the year 2000 IUCLID dataset for nonylphenol.)

Metal: In rabbits, barium nitrate causes severe eye irritation after a 24-hr exposure. (World Health Organization, 1990, Environmental Health Criteria 107 Barium)

Reliability :

Reference :

5.4 REPEATED DOSE TOXICITY

Type :

Guideline/method :

Species :

Strain :

Sex :

Number of animals :

Route of admin. :

Exposure period :

Frequency of treatment :

Post exposure period :

Doses :

Control group :

NOAEL :

LOAEL :

Other :

Year :

GLP :

Test substance :

Method :

Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Two repeated dose toxicity studies with rats, one 28-d and one 90-d, have been conducted on nonylphenol. In both studies, nonylphenol was administered in the diet. The NOAEL in the 28-d study was 100 mg/kg bw (Reference 64 in the year 2000 IUCLID dataset for nonylphenol). In the 90-d study, the NOAEL was 650 ppm in the diet, which was equivalent to an intake of 50 mg/kg bw (Cunney et al., 1997. Reg. Toxicol. Pharmacol. 26:172-178).

Metal: Several subchronic and chronic toxicity studies have been conducted on barium compounds in rats and mice. These studies provide evidence that the kidney, including glomerular damage, is a sensitive target of barium toxicity in rats and mice fed a nutritionally adequate diet (U.S. EPA 1999, Toxicological Review of Barium and Compounds). Hypertension has also been observed in studies in which rats were fed a marginally adequate diet, particularly one with inadequate calcium levels. Hypertension has been observed in humans who ingested high doses of barium compounds under occupational exposure conditions, but has not been observed in longer term human studies following oral exposure to lower concentrations of barium in drinking water (U.S. EPA 1999, Toxicological Review of Barium and Compounds).

The most significant repeated-dose study on barium exposed rats and mice to barium chloride dihydrate via drinking water (0, 500, 1250, or 2500 ppm) for approximately 2 years (NTP, 1994). For mice, the authors estimated the daily doses as 30, 75, and 160 mg Ba/kg-day for males, and 40, 90, and 200 mg Ba/kg-day for females. For rats, the estimated daily doses were 15, 30, and 60 mg Ba/kg-day for males, and 15, 45, and 75 mg Ba/kg-day for females. For the 2,500 ppm exposure group, survival rates for mice, but not for rats, were significantly decreased compared to controls. Nephropathy and other kidney effects were also observed in mice receiving the highest barium exposure; however, no chemical-related kidney lesions were observed in any of the rat treatment groups. The only potential sign of renal toxicity was an increase in relative kidney weight in female rats at 2,500 ppm. Based on these results, 75 mg Ba/kg-day was designated a chronic LOAEL and 45 mg Ba/kg-day a chronic LOAEL for female rats for renal effects in the NTP (1994) study. [Reference: National Toxicology Program (NTP). 1994. NTP Technical report on the toxicology and carcinogenesis studies of barium chloride dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). NTP TR 432. Research Triangle Park. NIH Pub. No. 94-3163. NTIS no. PB94-214178.]

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :
Cytotoxic concentr. :

Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Nonylphenol has been tested for genotoxicity in two in vitro test systems. Results were negative both with and without metabolic activation in both the Ames Assay and the HPGRT Assay. (References 65 and 66 in the year 2000 IUCLID dataset for nonylphenol.)

Metal: Most in vitro studies have found that barium chloride and barium nitrate did not induce gene mutations in bacterial assays with or without metabolic activation (in U.S. EPA 1999, Toxicological Review of Barium and Compounds). Ames assays with *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA97, TA98, and TA100 with or without metabolic activation (Monaco et al., 1990, 1991; NTP, 1994), rec assays with *Bacillus subtilis* strains H17 and H45 (Nishioka, 1975; Kanematsu et al., 1980), and a microscreen assay with *Escherichia coli* (Rossman et al., 1991) with metabolic activation have produced negative results with barium chloride. Negative results have also been observed for barium nitrate in the rec assay with *B. subtilis* strains H17 and H45 (Kanematsu et al., 1980). Barium chloride induced gene mutations in L5178Y mouse lymphoma cells with metabolic activation but not in the absence of metabolic activation (NTP, 1994). Neither barium acetate or barium chloride decreased the fidelity of DNA synthesis in avian myeleblastosis virus DNA polymerase (Sirover and Loeb, 1976). In mammalian cells, barium chloride did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without activation (NTP, 1994). (Note: All citations in this section are “as cited in” U.S. EPA 1999, Toxicological Review of Barium and Compounds)
Reliability :
Reference :

5.6 GENETIC TOXICITY ‘IN VIVO‘

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Nonylphenol did not produce mutagenic effects on erythrocytes in the mouse micronucleus assay when administered by gavage at a dose level of 500 mg/kg, the maximum tolerated dose. (Reference 67 in the year

level of 500 mg/kg, the maximum tolerated dose. (Reference 67 in the year 2000 IUCLID dataset for nonylphenol.)

Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The development toxicity and teratogenicity of nonylphenol has been studied in the rat. Nonylphenol administered daily by gavage to pregnant females on days 6 through 15 of gestation produced no abnormalities or other observable adverse effects on embryo-fetal development at dose levels as high as 300 mg/kg, although clear signs of maternal toxicity were observed at this level. (Reference 68 in the year 2000 IUCLID dataset for nonylphenol.)

Metal: A subchronic single-generation reproductive/developmental toxicity study did not find any significant alterations in gestational length, pup survival, or occurrence of external abnormalities in rats and mice exposed to barium chloride in drinking water at levels up to 2,000 ppm (Dietz et al., 1992 as cited in U.S. EPA 1999, Toxicological Review of Barium and Compounds). This study also did not find any significant alterations in reproductive endpoints in the Fo rats and mice; however, the low pregnancy rates in all groups, including controls, limit the usefulness of this study for determining an LOAEL.

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type	:
Guideline/method	:
In vitro/in vivo	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Duration of test	:
Doses	:
Control group	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:

Supporting data for dissociation products:
Acid: The reproductive effects of nonylphenol have been evaluated in a three-generation study with Sprague-Dawley rats. Nonylphenol was administered in the diet at concentrations of 0, 200, 650, and 2000 ppm (equivalent to an intake of about 0, 15, 50, and150 mg/kg/day during non-reproductive phases and rising to around 0, 30, 100, and 300 mg/kg/day during lactation). Parameters evaluated during the study included body weights, feed consumption, clinical observations, estrous cyclicity, reproductive performance, anogenital distance, pup survival, sexual development, sperm analysis, gross pathology, organ weights, and limited/selected histopathology. Terminal body weights were reduced in rats at the two highest exposure levels; however, feed consumption, clinical observations, and mortality were not adversely affected by nonylphenol administration. A treatment-related increase in the incidence of renal tubular degeneration/ dilatation was observed in males at all exposure levels (excluding controls) and females fed nonylphenol at 2000 ppm. No treatment-related changes were noted in litter data from all three mating trials, but based on decreased epididymal sperm density and testicular spermatid counts in males, and increased estrous cycle length and decreased ovarian weights observed in females, it was concluded that nonylphenol is a male and female reproductive toxicant at concentrations greater than or equal to 650 ppm in the diet (50 mg/kg/day). Overall, there was no dose level that did not produce effects, therefore, the LOEL in this study was 15 mg/kg/day based on kidney effects. (Reference: Final report on the reproductive toxicity of nonylphenol (CAS #84852-15-3) administered in diet to Sprague-Dawley rats. 1997. NTIS Technical Report NTIS/PB97-210900. NTP-RACB-94-021.)

Metal: A subchronic single-generation reproductive/developmental toxicity study did not find any significant alterations in gestational length, pup survival, or occurrence of external abnormalities in rats and mice exposed to barium chloride in drinking water at levels up to 2,000 ppm (Dietz et al., 1992 as cited in U.S. EPA 1999, Toxicological Review of Barium and Compounds). This study also did not find any significant alterations in reproductive endpoints in the Fo rats and mice; however, the low pregnancy rates in all groups, including controls, limit the usefulness of this study for

rates in all groups, including controls, limit the usefulness of this study for determining an LOAEL.

Reliability :
Reference :

20.0 OTHER INFORMATION

20.1 Estrogenic Effects

Supporting data for dissociation products:
Acid: The estrogenic activity of nonylphenol has been assessed in several in vitro and in vivo studies. Overall these studies show that nonylphenol has estrogenic activity of a potency that is between 3 to 6 orders of magnitude less than that of estradiol. Because estrogen antagonists can block it, the estrogenic effect appears to be mediated through the estrogen receptor. The structure of the aliphatic side chain (nonyl) is believed to be highly important for estrogenic activity. Linear nonylphenol is not estrogenic, while one or more of the branched chain isomers may be able to mimic estradiol in binding to the estrogen receptor. (Reference: Nielsen et al., 1999. Toxicological evaluation and limit values for nonylphenol, nonylphenol ethoxylates, tricresyl phosphates and benzoic acid. Danish Veterinary and Food Administration, Institute of Food Safety and Toxicology.)

6.2 Carcinogenicity

Supporting data for dissociation products:
Metal: A weight-of-evidence evaluation and cancer characterization has been performed for barium compounds in the Toxicological Review of Barium and Compounds conducted in support of summary information on the Integrated Risk Information System (IRIS)(U.S. EPA, 1999). Oral exposure studies in rats and mice did not find significant increases in tumor incidence following chronic exposure to barium compounds for up to two years (NTP, 1994; McCauley et al., 1985; Schroeder and Mitchener, 1975a,b). Inhalation exposure and intratracheal studies conducted by Tarasenko et al. (1977) were judged to be inadequate for carcinogenicity evaluation because of several deficiencies in design and reporting. Based on the available weight of evidence, it was concluded that under EPA's proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996) barium is considered not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure. (Note: All citations in this section are "as cited in" U.S. EPA 1999, Toxicological Review of Barium and Compounds)

1.0 SUBSTANCE INFORMATION

Generic Name	:	
Chemical Name	:	Fatty acids, tall oil, cobalt salts
CAS Registry No.	:	61789-52-4
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	
Molecular Weight	:	
Synonyms and Tradenames	:	Cobalt tallate; Tall oil fatty acids, cobalt salts
References	:	

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : For tall oil fatty acids, the boilingpoint is reproted as approx. 160 - 210 °C at 6.6 hPa. Union Camp Chemicals (Durham. UK); cited in year 2000 IUCLID dataset.
Reliability :
Reference :

2.3 DENSITY

Type : Specific gravity
Guideline/method :
Value : 1.02 at 25°C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference Material Safety Data Sheet for cobalt tallate, OMG Americas, Inc.

2.4 VAPOR PRESSURE

Type :
Guideline/method :
Value : hPa at °C

Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : For tall oil fatty acids, the vapor pressure is negligible at 25°C. Union Camp Chemicals (Durham. UK); cited in year 2000 IUCLID dataset.
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Data for Dissociation products:**
Acid: When tested according to OECD Test Method 117, at pH 2, the log P_{ow} values for seven compounds in tall oil fatty acid were 4.4, 7.0, 7.3, 7.5, 7.7, 8.0, and 8.3. At pH 7.5, the log P_{ow} values for six compounds in tall oil fatty acid were 3.6, 3.8, 4.2, 4.5, 4.7, and 7.4. Dybdahl, H.P. 1993. See robust summary in Appendix ?. For fatty acids, C16-C18 and C18 unsaturated, branched and linear the log P_{ow} was 4.90 (pH not specified). Mullee, D.M. 1994. See robust summary in attached document prepared by the Pine Chemicals Association.
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
PKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :

Result :
Remark :
Reliability :
Reference :

2.7 FLASH POINT

Type :
Guideline/method :
Value : °C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Halflife (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.2 Disssociation

Type : Dissociation constant determination
Guideline/method : OECD 112
pKa : 5.82 at 20°C
Year : 2002
GLP : Yes
Test substance : Cobalt tallate, CAS number 61789-52-4, received from OMG. Dark solid, purity of 20.6% cobalt
Approximate water solubility : 3.5 mg/L, determined by Inductively Coupled Plasma Atomic Emission Spectrometry during preliminary study
Method : OECD Guideline 112, Dissociation Constants in Water
Method detail : Three replicate samples of cobalt tallate were prepared at a nominal concentration of 1.5 mg/L by fortification of 100 mL of degassed water (ASTM Type II) with a 1.0 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.00025 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result : Mean (N = 3) pKa value was 5.82 (SD = 0.108) at 20°C
Remark : The results indicate that dissociation of the test substance will occur at

		environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference		Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of tall oil, cobalt salts, Wildlife International, Ltd. Study No. 534C-117, conducted for the Metals Carboxylate Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %
Control substance	:	
Kinetic	:	%

%

Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The biodegradability of tall oil fatty acids has been studied in several diferent tests. In a ready biodegradabiity closed bottle test (OECD 301D), the test material degraded 50% in 7 days and 56% in 28 days (Madsen, 1993). In a manometric respiratory test (OECD 301 F), the substance degraded 84% in 28 days (Aniol, 1999). In a ready biodegradability study (OPPTS 853.110), 74% of the test article degraded in 28 days (Sewell, 1994). See robust summaries in attached document prepared by the Pine Chemicals Association.
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The 96-h LC50 for zebrafish is reported to be 10 to 20 mg/L for tall oil fatty acids. Arizona Chemical Company letter to U.S EPA dated November 2, 1999. [Available from the National Techncial Information Service in microfiche OTS0559827, Initial submission letter from attorneys of Arizona Chemical Co. to USEPA regarding 17 health and ecotoxicity studies of various chemicals with attachments and dated 110299 (sanitized)]. **Metal:** For cobalt chloride, the 96-h LC50 was 333 mg Co/L for *Cyprinus carpio* and 1,406 mg Co/L for *Onchorynchus mykiss* (ECOTOX data base).
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:
Guideline/method	:
Species	:
Exposure period	:
NOEC	:
EC0	:
EC50	:
EC100	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:

Remark : **Supporting data for dissociation products:**
Acid: The 48-h EC50 for *Daphnia magna* is reported as 55.7 mg/L for tall oil fatty acids. Arizona Chemical Company letter to U.S EPA dated November 2, 1999. [Available from the National Techncial Information Service in microfiche OTS0559827, Initial submission letter from attorneys of Arizona Chemical Co. to USEPA regarding 17 health and ecotoxicity studies of various chemicals with attachments and dated 110299 (sanitized)].
Metal: For cobalt chloride, the reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base).

Reliability :

Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :

Guideline/method :

Species :

Endpoint :

Exposure period :

NOEC :

LOEC :

EC0 :

EC10 :

EC50 :

Other :

Other :

Other :

Limit test :

Analytical monitoring :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark : **Supporting data for dissociation products:**
Acid: The growth inhibition EC50 values for three algal species were reported to range from 0.79 to 9 mg/L for tall oil fatty acids. Arizona Chemical Company letter to U.S EPA dated November 2, 1999. [Available from the National Techncial Information Service in microfiche OTS0559827, Initial submission letter from attorneys of Arizona Chemical Co. to USEPA regarding 17 health and ecotoxicity studies of various chemicals with attachments and dated 110299 (sanitized)].
Metal: For cobalt chloride, the 96-h EC50 for *Chorella vulgaris* was 0.522 mg Co/L (ECOTOX data base).

Reliability :

Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo :
Type :
Guideline/method :
Species :
Number of animals :
Males :
Females :
Doses :
Males :
Females :
Vehicle :
Route of administration :
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behavior :
Deg. product :
Deg. products CAS# :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. Clin. Tox. 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :

Guideline/Method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability : **Supporting data for dissociation products:**
Acid: The acute oral LD50 of tall oil fatty acids has been reported as >10,000 mg/kg in rats using a test procedure consistent with OECD Test Method 401. Mallory, 1983. See robust summary in attached document prepared by the Pine Chemicals Association.
Metal: Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg CoCl2/kg bw (equivalent to 19.1 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate is reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 55.4 to 72.5 mg Co/kg bw) (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 55.4 mg/kg bw when expressed as cobalt (ATSDR Sept 2001 Draft).
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m3 as mixed cobalt oxides. (ASTDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was > 10 mg/L (IUCLID, 2000).

Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Cobalt is reported to be irritating to the skin (IUCLID, 2000)
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :

Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Two repeated dose oral toxicity studies in rats have been conducted using tall oil fatty acids. In a 28-d dietary feeding study, the NOAEL was 15% when expressed in terms of total calories fed (Seppanen, 1969). Growth was significatnly decreased at a feeding level of 30% of total calories. In a 90-d dietary feeding study, the NOEL was 5% in the diet or approximately 2,500 mg/kg/day (Fancher, 1969). The most sensitive effect was a reduction food consumption (but not body weight) at 10% in the diet. No effects on clinical signs or histopathology were reported at feeding levels up to 25% in the diet. See robust summary in attached document prepared by the Pine Chemicals Association.
Metal: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from

12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :
Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Tall oil fatty acids have tested negative in the Ames *Salmonella*/microsome plate test both with and without metabolic activation (Gedek, 1983). Testing was conducted with five different strains of S. Typhimurium at doses up to 10,000 µg/plate. See robust summary in attached document prepared by the Pine Chemicals Association.
Metal: Cobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be non-mutagenic in bacterial assays, but cobalt compounds with a valence state of III were weakly mutagenic (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :

Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (as cobalt chloride) (NOEL) (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type	:	
Guideline/method	:	
In vitro/in vivo	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid:** The effects of tall oil fatty acids on rat reproductive parameters have been studied in a two-generation feeding study (Tegeris, 1975). Feeding levels were 0, 5, or 10% in the diet. The parental (F_0) generation was fed the test substance for approximately three weeks prior to mating. Following weaning, the F_1 generation was fed the test article for approximately 180 days prior to mating. Treatment did not affect the number of liveborn or stillborn F_1 litters and pups, or F_1 waning weight. No treatment-related changes in fertility, viability, lactation, or gestation indices were measured. Clinical chemistry and pathological examinations also did not reveal treatment-related effects. See robust summary in attached document prepared by the Pine Chemicals Association. **Metal:** Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

21.0 OTHER INFORMATION

Supporting data for dissociation products:
Acid: A safety assessment of tall oil acid (a purified form of tall oil fatty acids) has been performed for use in cosmetic products by an Expert Panel (Expert Panel, 1989). Based on its review of available data for tall oil acid and its primary constituent (oleic acid), the Expert Panel concluded that tall oil acid is safe for use in cosmetics. The Expert Report includes a clinical assessment of safety for dermal exposure based on testing in human subjects. Several studies were conducted with liquid soaps containing 12% tall oil acid. These studies included a 4-week hand washing study with a diluted soap (final concentration of 3% tall oil acid) and two repeated dose patch studies with undiluted soap. None of the subjects in these studies had positive reactions and the soap was found to be non-irritating and non-sensitizing.

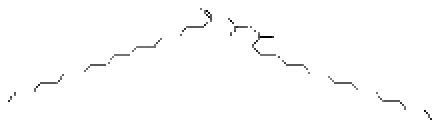
Expert Panel. 1989. Final report on the safety assessment of tall oil acid. J. Amer. Coll. Toxicol. 8:769-776.

21.1 CARCINOGENICITY

Supporting data for dissociation products:
Metal: The US National Toxicology Program does not recognize cobalt as a human carcinogen, but IARC has classified cobalt and cobalt compounds as possibly carcinogenic to humans (Class 2B) based on sufficient evidence that cobalt metal powder and cobaltous oxide are carcinogenic in animals (Barceloux 1999, ATSDR Sept 2001 Draft). “No studies were located regarding carcinogenic effects in animals after oral exposure to stable [non-radioactive] cobalt.” (ATSDR Sept 2001 Draft)

1.0 SUBSTANCE INFORMATION

Generic Name	:	Aluminum distearate
Chemical Name	:	
CAS Registry No.	:	300-92-5
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$Al(OH)(C_{18}H_{35}O_2)_2$



Molecular Weight	:	610.94
Synonyms and Trade names	:	Aluminum Hydroxide Distearate; Aluminum Hydroxybis (octadecano-o)-; Aluminum, Hydroxybis (Stearato)-; Aluminum, Hydroxydistearate.
References	:	Cosmetic, Toiletry and Fragrance Association (1982) Final Report of the Safety Assessment of Lithium Stearate, Aluminum Stearate, Aluminum Tristearate, Ammonium Stearate, Calcium Stearate, Magnesium Stearate, Potassium Stearate, Sodium Stearate, and Zinc Stearate. J. A. Coll. Toxicol. 1 (2): 143-177. Subsequently called CTFA #9).

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	145 °C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: The melting point reported for stearate is 69.7°C (Appendix 1).
Reliability	:	[4] Reliability unknown, insufficient information
Reference	:	HSDB (2002) Hazardous Substances Databank, National Library of Medicine (http://toxnet.nlm.nih.gov)[HSDB/29]

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	°C at hPa
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: The reported range for stearate is 376-383 °C (Appendix 1).
Reliability	:	
Reference	:	

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	1.009 at °C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: Reported value for stearate is 0.9408 at 20°C (HSDB 8/16/02).
Reliability	:	[4] Unassignable, insufficient information
Reference		HSDB/29

2.4 VAPOR PRESSURE

Type	:	

Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: 1.0 hPa at174°C (Appendix 1).
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: Log Kow for stearate is reported as 8.2 at 25°C (Appendix 1).
Reliability	:	[4] Unassignable, insufficient information
Reference	:	HSDB/29

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	Insoluble in water
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: The reported values for stearate are 0.60 mg/L at 25 °C and 2.9 mg/L at 25 °C (Appendix 1).
Reliability	:	[4] Unassignable, insufficient information

Reference	:	HSDB/29

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type
Guideline/method :
Light source :
Light spectrum :
Relative intensity : based on
Spectrum of substance : lambda (max, >295nm) :
epsilon (max) :
epsilon (295) :
Conc. of substance : at °C
DIRECT PHOTOLYSIS
Half-life (t1/2) :
Degradation : % after
Quantum yield :
INDIRECT PHOTOLYSIS
Sensitizer :
Conc. of sensitizer :
Rate constant :
Degradation :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.2 DISSOCIATION

Type :
Guideline/method :
pKa :
Year :
GLP :
Test substance :
Approximate water solubility :
Method :
Method detail :
Result :
Remark : Dissociation could not be evaluated for this compound due to the low solubility.
Reliability :
Reference :
Type :
Guideline/method :
pKa :

Year :

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration :
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculums :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %
%
Deg. product :
Year :
GLP :
Test substance :

Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Stearate is readily biodegradable: 72% in 28 days (Appendix 1)
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
LC0 :
LC50 :
LC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: 48-h LC50 for *C. carpio* > 1000 mg/L; NOEC ≥ 1000 mg/L (Appendix 1).

Metal: For a test with aluminum chloride, the 96-hr LC50 was 27.1 mg Al/L for *Gambusia affinis* (mosquitofish) (Reference 508 in the ECOTOX database). For a test with aluminum chloride, the 48-hr LC50 was 80 mg Al/L for *Danio rerio* (zebrafish) (Reference 11199 in the ECOTOX database). For a test with aluminum chloride, the 96-hr LC50 was 8.6 mg Al/L for *Oncorhynchus mykiss* (rainbow trout) (Reference 3689 in the ECOTOX database).

Reliability :
Reference :

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
EC0 :
EC50 :
EC100 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :

Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: For stearate 47-h NOEC *Daphnia magna* ≥ 0.09 mg/L (solubility limit) (Appendix 1).
Metal: For aluminum chloride, the 48-hr EC50 for *Daphnia magna* ranged from 3.9 to 27.3 mg Al/L in three different tests (IUCLID, 2000). The 48-hr LC0 for the eastern oyster, *Crassotrea virginica*, was 7.5 mg Al/L (IUCLID, 2000). The most sensitive invertebrate to aluminum chloride is the marine worm *Ctenodrillus serratus* with a 96-hr LC50 of 0.097 mg Al/L (Reference 2146 in the ECOTOX database).
Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: For stearate the 72-h EC50 >1016 mg/L for *Scenedesumus subspicatus*; NOEC = 1016 mg/L (Appendix 1).
Metal: Effects on the algae *Scenedesmus quadricauda* are seen at levels of 1.5 to 2.0 mg Al/L in 4-day tests with aluminum chloride (IUCLID, 2000). Effects on the population growth of *Chlorella vulgaris* were seen at a level of 0.225 mg/L in a 4-month study with aluminum chloride (IUCLID, 2000).
Reliability :
Reference :

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on Acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:**

Metal: Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Approximately 0.1% of ingested aluminum is usually absorbed, although absorption of the more bioavailable forms can be on the order of 1%. The unabsorbed aluminum is excreted in the feces. The 10-fold range in absorption of aluminum is due to differences in bioavailability related to the form of ingested aluminum (type of anion) and the presence of dietary constituents which can complex with aluminum and thereby enhance or inhibit its absorption. In acidic conditions such as the stomach (pH≈2) aluminum occurs primarily as a monomolecular hexahydrate, $Al(H_20)_6^{+3}$, which is generally abbreviated as Al^{+3} and referred to as “free” aluminum. As pH increases, a series of aluminum hydroxy complexes are formed by successive deprotonation so that, in near neutral conditions such as the intestines, the predominant form is aluminum hydroxide, $Al(OH)_3$, an insoluble precipitate. The acidic conditions and mixing/residence time in the stomach appear to

ensure that the majority of consumed aluminum will be solubilized to monomolecular aluminum (most likely free Al^{+3}), regardless of the compound and form (e.g., food, drinking water, antacid tablets) in which it was ingested. The solubilized aluminum that is in the stomach can recomplex with the anion from the original aluminum compound that was ingested or form new complexes with dietary ligands. The dietary ligands that appear to play an important role in the complexation process include simple mono-, di-, and tricarboxylic acids (particularly citric acid). The vast majority of desolubilized aluminum is not complexed, is rapidly precipitated as insoluble (unabsorbable) aluminum hydroxide in the duodenum by the near–neutral pH conditions, and is ultimately excreted in the feces. (Text from Agency for Toxic Substances and Disease Registry [ATSDR] 1999, Toxicological Profile for Aluminum)

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :
Guideline/Method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Rat LD50 > 2000 mg/kg bw for stearate(Appendix 1).Male rats (5 males per treatment) were dosed with 0.464 to 10.0 g/kg of eutectic (triple pressed) stearic acid. The LD50 was reported as >10.0 g/kg.
Reference: Cosmetic, Toiletries, and Fragrance Association (1987) Cosmetic Ingredient Review, Final Report on the Safety Assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid and Stearic Acid. J. Am. Coll. Toxicol. Vol. 6, No. 3, pp321-401. (Subsequently referred to as CTFA#3.)

Metal: The rat oral LD50 for aluminum chloride has been reported to range from 380 to 3,730 mg/kg bw, with several values in the 3,300 to 3,700 mg/kg bw range. Mouse LD50 values for aluminum chloride range from 770 to 3,805 mg/kg bw. (IUCLID, 2000)

Reliability :
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Stearic acid, 10-100 mM in olive oil was dosed intradermally in guinea pigs and rabbits which resulted in mild erythema and slight induration of skin. CTFA#3 ref 157. Stearic acid as a 20% formulations was applied at 2.0 ml/kg of product to abraded/intact sites on the backs of rabbits. After four weeks no mortalities and slight edema and sesqumation were observed. CTFA#3 ref 163.
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	PII = 0.06 (Max. = 8)
Year	:	
GLP	:	
Test substance	:	10% Suspension in corn oil
Method	:	
Method detail	:	Material applied in a single exposure under occlusive conditions
Result	:	Minimal irritation
Remark	:	**Supporting data for dissociation products:** **Metal**: Solutions of 2.5 to 5.0 % aluminum chloride hexahydrate are mildly to moderately irritating to human skin when applied once daily for 3 days. (IUCLID, 2000)
Reliability	:	[4] Unknown Reliability, Insufficient information
Reference	:	CTFA#3

5.2.2 EYE IRRITATION

Type	:	Draize
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	10% Suspension in corn oil
Method	:	Draise
Method detail	:	Eyes were unrinsed
Result	:	Scores were 1, 1, and 0 on days 1, 2, and 3. Minimal irritation
Remark	:	**Supporting information for dissociation products:** **Acid:** Stearic acid (eutatectic, commercial grade) applied to the eyes of albino rabbits following the Draise method. Results ranged from no irritation to mild conjunctival erythema in 2 rabbits subsiding by 72 hours. Stearic acid in various formulations at lower strengths showed similar results (CTFA#3).
Reliability	:	[4] Unassignable, Insufficient information
Reference	:	

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: LOAEL was 3000 ppm based on mortality. (Appendix 1Chronic feeding studies with rats exposed to stearic acid have shown reversible effects with no significant pathological lesions. Animals fed for 24 weeks with stearic acid (50g/kg/day) developed foreign body type reaction in perigenital fat. Lipogranulomas were observed to be reversible. Rats fed stearic acid (3000 ppm) for 30 weeks developed anorexia, severe pulmonary infection, high mortality. No significant pathological lesions were observed. (CTFA#3 ref 151,152., Appendix 1).

Metal: Neurotoxicity is the most sensitive endpoint that has been identified in repeated dose toxicity studies with aluminum compounds (ATSDR 1999, Toxicological Profile for Aluminum). Neurobehavioral impairments have been identified in orally exposed adults, as well as weanlings and young animals exposed by several different routes (e.g., gestation, lactation, ingestion, and combinations thereof). The most frequently observed behaviors in adult mice (the most sensitive species) include decreases in motor activity, grip strength, and startle responsiveness. In weanlings and young mice, the most common effects are increases in grip strength and landing foot splay, and decreased thermal sensitivity. The Minimum Risk Level (MRL) for aluminum derived by the Agency for Toxic Substances and Disease Registry (ATSDR) is based on a NOAEL of 62 mg Al/kg/day determined in a study by Golub et al. (1989) with adult mice exposed to dietary aluminum lactate for 6 weeks (ATSDR 1999, Toxicological Profile for Aluminum). The LOAEL in this study was 130 mg Al/kg/day based on decreased spontaneous motor activity.
Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :

Species :
Strain :
Test concentrations :
Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Not mutagenic in *S. typhimurium* with and without metabolic activation (Appendix 1). Stearic acid was tested for mutagenicity using the Ames test with *Salmonella typhumurium* strains TA98, TA100, TA1535, TA1537, TA1538. Spot tests were performed suing 50 mg/ml Stearic acid suspensions in the distilled waster (50 µg/plate) with and without microsomal activation from hepatic S9 fractions from rats induced with Aroclor 1254 (50 µg/plate). Positive controls were 2-aminoanthracene and 4-nitro—o-phenylenediamine in dimethyl sulfoxide, 9-aminoacridinein ethanol, and sodium azide in distilled water with and without metabolic activation. (CTFA#3.)

Metal: It appears that aluminum can cause genotoxicity under some circumstances, although most study data indicate that aluminum does not directly interact with DNA in mutagenicity tests (ATSDR 1999, Toxicological Profile for Aluminum). Negative mutagenicity data come from transformation assays in Syrian hamster cells (DiPaola and Casto, 1979), recombination repair assays in *Bacillus subtilis* (Kanematsu et al., 1980), and Ames assays with *Salmonella typhimurium* (Marzin and Phi, 1985). Genotoxicity has been demonstrated in an *in vitro* study that showed aluminum chloride to cause cross-linking of chromosomal proteins and DNA in ascites hepatoma cells from Sprague-Dawley rats (Wedrychowski et al., 1986). Micromolar aluminum concentrations have also been shown to reduce ^{3}H-thymidine incorporation in a transformed cell line (Blair et al., 1989), suggesting that aluminum may impede cell cycle progression; however, the results have not been verified in normal, untransformed cells. [Note: all citations are from ATSDR 1999, Toxicological Profile for Aluminum.]

Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :

Sex	:	
Route of admin.	:	
Exposure period	:	
Doses	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal**: Data from an in vivo study with mice indicate that aluminum chloride is clastogenic when dosed via an intraperitoneal injection, causing an increase in chromatid-type aberrations in bone marrow cells (Manna and Das 1972 as cited in ATSDR 1999, Toxicological Profile for Aluminum). Although no dose-response relationship was found in this study, the highest dose of aluminum chloride did produce the greatest number of aberrations.
Reliability	:	
Reference	:	

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
NOAEL maternal tox.	:	
NOAEL teratogen.	:	
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** Developmental toxicity studies in animals have shown that oral exposure to aluminum induced skeletal variations such as delayed ossification in rats and mice under conditions that enhance its uptake, particularly maternal intake of compounds that are highly bioavailable (e.g., aluminum citrate and nitrate), concurrent exposure to dietary constituents that contribute to increased absorption of aluminum (e.g., citrate), and/or bolus administration by gavage (ATSDR 1999, Toxicological Profile for Aluminum). Given the relatively high

bioavailability of the developmentally toxic forms of aluminum and bolus administration, it is possible that the skeletal changes are consequent to phosphate depletion caused by excess binding with aluminum in the maternal gut. Neurobehavioral deficits have been observed on oral studies with weanlings and young developing mice and rats exposed to aluminum by gestation, combined gestation and lactation, combined gestation and lactation followed by postweanling ingestion, and postweanling ingestion alone. The most frequently affected behaviors in exposed weanlings and young animals included increases in grip strength and landing foot splay, decreased thermal sensitivity, and negative geotaxis. Teratogenic changes have not been associated with gestational exposure to aluminum. (Text from ATSDR, 1999, Toxicological Profile for Aluminum)

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Metal: Oral studies in male and female animals show some inconsistencies, but generally indicate that reproductive toxicity is not an effect of concern for aluminum-exposed people (ATSDR 1999, Toxicological Profile for Aluminum). Mating success (numbers of litters and offspring) was not affected in a three-generation study with Dobra voda mice that were exposed to 49 mg Al/kg/day in drinking water and base diet over a period of 180 to 390 days (Ondriecka et al., 1966). No reproductive effects were observed in pregnant Swiss Webster mice that consumed 250 mg al/kg/day as aluminum lactate throughout gestation and lactation (Golub et al., 1992a). An increased incidence of resorptions occurred in mice that were gestationally exposed to aluminum chloride by gavage (Crammer et al., 1986), but no reproductive effects were found in rats similarly exposed to

aluminum chloride, hydroxide, or citrate (Gomez et al., 1991; Miswa and Shigeta, 1992). [Note: all citations are from ATSDR 1999, Toxicological Profile for Aluminum.]

Reliability :

Reference :

22.0 OTHER INFORMATION

22.1 Carcinogenicity

Supporting information for dissociation products:
Metal: Aluminum and aluminum compounds are not known to cause cancer in humans. Although some workers in the aluminum industry have had a higher than expected cancer mortality rate, all indications are that this is due to pitch fume or other carcinogens to which they are exposed, and not due to the presence of aluminum compounds (IARC, 1984). There are several cancer studies on animals in the scientific literature. None of these studies show that aluminum is carcinogenic (Hackenberg 1972; Oneda et al 1994; Pigott et al 1981; Schroeder and Mitchener 1975a, 1975b). [Note: all citations are from ATSDR 1999, Toxicological Profile for Aluminum.]

6.2 Skin Sensitization

Supporting information for dissociation products:
Metal: Aluminum chloride has not been shown to cause skin sensitization in the guinea pig using either the Buehler test or the Maximization test, or in the mouse using the Ear Swelling Test (IUCLID, 2000).

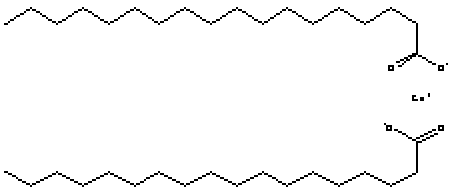
1. General Information

ID

Date December 20, 2002

1.0 SUBSTANCE INFORMATION

Generic Name	:	Cobalt Stearate
Chemical Name	:	
CAS Registry No.	:	13586-84-0
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$Co(C_{18}H_{35}O_2)_2$



Molecular Weight	:	
Synonyms and Tradenames	:	Octadecanoic acid, cobalt salt, stearic acid, cobalt salt
References	:	MSDS, http://www.icnbiomedical.com

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The melting point reported for stearate is 69.7°C (Appendix 1).
Reliability :

Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The reported range for stearate is 376-383 °C (Appendix 1).
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Reported value for stearate is 0.9408 at 20°C (HSDB 8/16/02).
Reliability :
Reference

2.4 VAPOR PRESSURE

Type :
Guideline/method :

Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: 1.0 hPa at174°C (Appendix 1).
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: Log Kow for stearate is reported as 8.2 at 25°C (Appendix 1).
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: The reported values for stearate are 0.60 mg/L at 25 °C and 2.9 mg/L at 25 °C (Appendix 1).
Reliability	:	
Reference	:	

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	7.50 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Cobalt stearate, lot number F26L13, received from Alfa Aesar. Dark pellets, purity of 9.6% cobalt.
Approximate water solubility	:	0.17 mg/L, determined by Inductively Coupled Plasma Atomic Emission Spectrometry during preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water

Method detail	:	Three replicate samples of cobalt stearate were prepared at a nominal concentration of 0.10 mg/L by fortification of 100 mL of degassed water (ASTM Type II) with a 0.10 mg/mL stock solution of the test substance in tetrahydrofuran. Each sample was titrated against 0.00025 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.
Result	:	Mean (N = 3) pKa value was 7.50 (SD = 0.0356) at 20°C
Remark	:	The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).
Reliability	:	[1] Reliable without restriction.
Reference	:	Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of cobalt stearate, Wildlife International, Ltd. Study No. 534C-113, conducted for the Metals Carboxylate Coalition.

3.2.1 MONITORING DATA

Type of measurement	:	
Media	:	
Concentration	:	
Substance measured	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.3.1 TRANSPORT (FUGACITY)

Type	:	
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Year	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.5 BIODEGRADATION

Type	:	
Guideline/method	:	
Inoculum	:	
Concentration	:	related to related to
Contact time	:	
Degradation	:	(±) % after day(s)
Result	:	
Kinetic of test subst.	:	% (specify time and % degradation) % % % %
Control substance	:	
Kinetic	:	% %
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: Stearate is readily biodegradable: 72% in 28 days (Appendix 1)
Reliability	:	
Reference	:	

3.7 BIOCONCENTRATION

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	at °C
Concentration	:	
BCF	:	
Elimination	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Acid:** 48-h LC50 *C. carpio* > 1000 mg/L; NOEC ≥ 1000 mg/L (Appendix 1). **Metal:** For cobalt chloride, the 96-h LC50 was 333 mg Co/L for Cyprinus carpio and 1,406 mg Co/L for Onchorynchus mykiss (ECOTOX data base).
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Acid:** For stearate 47-h NOEC *Daphnia magna* ≥ 0.09 mg/L (solubility limit) (Appendix 1). **Metal:** For cobalt chloride, the reported 48-h EC50 values for *Daphnia magna* range from 1.11 to 5.6 mg Co/L (ECOTOX data base).
Reliability	:	
Reference	:	

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	
Guideline/method	:	
Species	:	
Endpoint	:	
Exposure period	:	
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Acid:** For stearate the, 72-h EC50 >1016 mg/L (*S. Subspicatus*); NOEC = 1016 mg/L (Appendix 1). **Metal:** For cobalt chloride, the 96-h EC50 for *Chorella vulgaris* was 0.522 mg Co/L (ECOTOX data base).
Reliability	:	
Reference	:	

4.4 CHRONIC TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

4.5 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type	:
Guideline/method	:
Species	:
Exposure period	:
NOEC	:
LOEC	:
EC0	:
EC50	:
EC100	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	:
Reliability	:
Reference	:

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** Absorption of cobalt in the digestive tract is influenced by the chemical form of the metal. The soluble form, cobalt chloride, is absorbed 13-34% in the gut of rats, but absorption in the gut may be increased in iron deficient individuals. The highest concentration of absorbed cobalt is in the liver and then the kidney. There is no accumulation of cobalt with age. Following oral exposure, cobalt is eliminated primarily in feces and secondarily in urine. For the more soluble forms of cobalt, e.g., cobalt chloride, 70 – 80% of the administered dose is eliminated in the feces. For absorbed cobalt, elimination is rapid primarily in the urine (Barceloux, D.G. (1999) Cobalt. Clin. Tox. 37(2):201-206). Elimination is biphasic or triphasic. The terminal phase involves a very small residual level of cobalt and has a half-life in years (ATSDR Sept 2001 Draft Toxicological Profile for Cobalt, U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry) (Subsequently listed as ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	
Guideline/Method	:	
Species	:	Rat
Strain	:	

Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Rat LD50 > 2000 mg/kg bw for stearate(Appendix 1).Male rats (5 males per treatment) were dosed with 0.464 to 10.0 g/kg of eutectic (triple pressed) stearic acid. The LD50 was reported as >10.0 g/kg.
Reference: Cosmetic, Toiletries, and Fragrance Association (1987) Cosmetic Ingredient Review, Final Report on the Safety Assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid and Stearic Acid. J. Am. Coll. Toxicol. Vol. 6, No. 3, pp321-401. (Subsequently referred to as CTFA#3.)

Metal: Acute oral toxicity values of the cobalt portion of the cobalt salts in this category are compared to simple cobalt salts such as cobalt chloride and cobalt sulfate. Reported LD50s of cobalt chloride to rats range from 42.4 to 190 mg CoCl2/kg bw (equivalent to 19.1 to 85.5 mg Co/mg bw) (ATSDR Sept 2001 Draft). Toxicity of cobalt sulfate reported to be similar to the chloride with the oral LD50s for rats ranging from 123 to 161 mg/kg bw (equivalent to 55.4 to 72.5 mg Co/kg bw) (ATSDR Sept 2001 Draft). For the mouse, LD50 values were reported as 89.3 and 123 mg/kg for cobalt chloride and the cobalt sulfate, respectively, which are equivalent to 40.2 and 55.4 mg/kg bw when expressed as cobalt (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: The acute LC50 for a 30-minute inhalation exposure in rats was 165 mg cobalt/m3 as mixed cobalt oxides. (ASTDR, 1992, Toxicological Profile for Cobalt). In a 1 hour exposure to a dust aerosol of cobalt powder, the LC50 for rats was > 10 mg/L (IUCLID, 2000).

Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Stearic acid, 10-100 mM in olive oil was dosed intradermally in guinea pigs and rabbits which resulted in mild erythema and slight induration of skin. CTFA#3 ref 157. Stearic acid as a 20% formulations was applied at 2.0 ml/kg of product to abraded/intact sites on the backs of rabbits. After four weeks no mortaltities and slight edema and sesqumation were observed. CTFA#3 ref 163.
Metal: Increased proliferation of lymphatic cells was seen in mice and guinea pigs dermally exposed to cobalt chloride, with LOAEL values ranging from 9.6 to 14.7 mg Co/kg/day. (ATSDR Sept 2001 Draft).
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: Cobalt is reported to be irritating to the skin. (IUCLID, 2000)
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Concentration	:	
Dose	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
Classification	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	**Supporting information for dissociation products:** **Acid:** Stearic acid (eutatectic, commercial grade) applied to the eyes of albino rabbits following the Draise method. Results ranged from no irritation to mild conjunctival eryhtema in 2 rabbits subsiding by 72 hours. Stearic acid in various formulations at lower strengths showed similar results (CTFA#3).
Remark	:	
Reliability	:	
Reference	:	

5.4 REPEATED DOSE TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Post exposure period	:	
Doses	:	
Control group	:	
NOAEL	:	
LOAEL	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Acid:** LOAEL was 3000 ppm based on mortality. (Appendix 1. Chronic feeding studies with rats exposed to stearic acid have shown reversible effects with no significant pathological lesions. Animals fed for 24 weeks with stearic acid (50g/kg/day) developed foreign body type reaction in perigenital fat. Lipogranulomas were oberved to be reveresible. Rats fed

perigenital fat. Lipogranulomas were oberved to be reveresible. Rats fed stearic acid (3000 ppm) for 30 weeks developed anorexia, sever pulmonary infection, high high m ortality.No significant pathological lesions were observed. (CTFA#3 ref 151,152., Appendix 1).
Metal: Repeated oral dosing of rats with cobalt chloride at levels ranging from 0.5 to 30.2 mg Co/kg/day (as cobalt chloride) for periods ranging from 12-16 days up to 7 months resulted in the following observations associated with LOAELs: reduced weight gain, increases in some organ weights (heart, liver and lungs); increased hematocrit, hemoglobin, and RBCs; renal tubular necrosis; and various changes on cardiac physiology (left ventricular hypertrophy, impaired ventricular function, and degeneration of myofibrils) (ATSDR Sept 2001 Draft). Cardiac effects were observed in rats at LOAEL's ranging from 8.4 to 12.4 mg Co/kg/day, for cobalt sulfate or cobalt chloride, with exposure periods of 3 weeks to 6 months (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :
Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Not mutagenic in *S. typhimurium* with and without metabolic activation (Appendix 1). Stearic acid was tested for mutagenicity using the Ames test with Salmonella typhumurium strains TA98, TA100, TA1535, TA1537, TA1538. Spot tests were performed suing 50 mg/ml Stearaic acid suspensions in the distilled waster (50 µg/plate) with and without microsomal activation from hepatic S9 fractions from rats induced with Aroclor 1254 (50 µg/plate). Positiive controls were 2-aminoanthracene and 4-nitro—o-phenylenediamine in dimethyl sulfoxide, 9-aminoacridinein ethanol, and sodium azide in distilled water with and without metabolic acitivation. (CTFA#3.)
MetalCobalt compounds with a valence state of II, the form of cobalt released by dissociation of cobalt salts, are reported to be generally non-mutagenic in bacterial assays, but increased frequency of genetic conversions have been reported in yeast. Cobalt compounds with a valence state of III were weakly mutagenic in bacterial systems (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Doses	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** Cobalt compounds, including salts, are observed to be genotoxic or mutagenic in mammalian systems. Cobalt compounds, including cobalt salts, are reported to be clastogenic in mammalian cells. Increased micronucleus formation was observed following i.p. injection of 12.4 and 22.3 mg Co/kg (as cobalt chloride), but not after injection of 6.19 mg Co/kg (as cobalt chloride) (NOEL) (ATSDR Sept 2001 Draft).
Reliability	:	
Reference	:	

5.8.2 DEVELOPMENTAL TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Route of admin.	:	
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	
Control group	:	
NOAEL maternal tox.	:	
NOAEL teratogen.	:	
Other	:	
Other	:	
Other	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** In a single developmental toxicity study with cobalt chloride exposure (5.4 or 21.8 mg Co/kg/day) from gestation day 14 to lactation day 21 the LOAEL was based on stunted pup growth. However, maternal toxicity was observed in conjunction with effects on the offspring. This growth effect was considered to be a secondary or indirect effect rather than a direct effect of cobalt on the fetus. No teratogenic effects were observed. Another study in rats provided a NOAEL of 24.8 mg Co/kg/day for cobalt chloride exposure from gestation days 6-15. No effects on fetal

for cobalt chloride exposure from gestation days 6-15. No effects on fetal growth or survival in mice exposed to 81.7 mg Co/kg/day as cobalt chloride during gestation days 8-12 (ATSDR Sept 2001 Draft).

Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Metal: Testicular degeneration and atrophy have been reported in rats exposed to 13.2 to 30.2 mg Co/kg/day as cobalt chloride for 2-3 months in the diet or drinking water. (ATSDR Sept 2001 Draft). Similar effects were seen in mice exposed to 23 to 43.4 mg Co/kg/day as cobalt chloride in drinking water for 10-13 weeks. In addition, reduced numbers of pregnant females and pups per litter, and reduced fertility, were observed in mice at 58.9 mg Co/kg/day. (ATSDR Sept 2001 Draft).

Reliability :
Reference :

23.0 OTHER INFORMATION

23.1 CARCINOGENICITY

Supporting information for dissociation products:

1. General Information

ID 6865-35-6

Date December 20, 2002

1.0 SUBSTANCE INFORMATION

Generic Name	:	Barium Stearate
Chemical Name	:	
CAS Registry No.	:	6865-35-6
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$Ba(C_{18}H_{35}O_2)_2$

Molecular Weight	:	
Synonyms and Tradenames	:	Octadecanoic acid, barium salt, stearic acid, barium salt
References	:	MSDS, http://www.icnbiomedical.com

2.1 MELTING POINT

Type :
Guideline/method :
Value : °C
Decomposition : at °C
Sublimation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The melting point reported for stearate is 69.7°C (Appendix 1)
Reliability :

Reference :

2.2 BOILING POINT

Type :
Guideline/method :
Value : °C at hPa
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result : **Supporting data for dissociation products:**
Acid: The reported range for stearate is 376-383 °C (Appendix 1)
Remark :
Reliability :
Reference :

2.3 DENSITY

Type :
Guideline/method :
Value : 1.13
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Reported value for stearate is 0.9408 at 20°C (HSDB 8/16/02)
Reliability :
Reference Shepard MSDS

2.4 VAPOR PRESSURE

Type :

Guideline/method	:	
Value	:	hPa at °C
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for pissociation products:** **Acid**: 1.0 hPa at174°C (Appendix 1)
Reliability	:	
Reference	:	

2.5 PARTITION COEFFICIENT

Type	:	
Guideline/method	:	
Partition coefficient	:	
Log Pow	:	at °C
pH value	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: Log Kow for stearate is reported as 8.2 at 25°C (Appendix 1)
Reliability	:	
Reference	:	

2.6.1 SOLUBILITY IN WATER

Type	:	
Guideline/method	:	
Value	:	0.004g/100ml (40 mg/L)
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
PKa	:	at °C
Description	:	
Stable	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	[4] Reliability unknown, insufficient information
Reference	:	MSDS, http://www.icnbiomedical.com

2.7 FLASH POINT

Type	:	
Guideline/method	:	
Value	:	°C
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Halflife (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 Dissociation

Type	:	Dissociation constant determination
Guideline/method	:	OECD 112
pKa	:	6.71 at 20°C
Year	:	2002
GLP	:	Yes
Test substance	:	Barium stearate, lot number 39411, received from Witco Company. White powder, purity of 20.6% barium.
Approximate water solubility	:	3.5 mg/L, determined by Inductively Coupled Plasma Atomic Emission Spectrometry during preliminary study
Method	:	OECD Guideline 112, Dissociation Constants in Water

Method detail : Three replicate samples of barium stearate were prepared at a nominal concentration of 1.5 mg/L by fortification of 100 mL of degassed water (ASTM Type II) with a 1.0 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.00025 N sodium hydroxide while maintained at a test temperature of 20±1°C. At least 10 incremental additions were made before the equivalence point and the titration was carried past the equivalence point. Values of pK were calculated for a minimum of 10 points on the titration curve. Phosphoric acid and 4-nitrophenol were used as reference substances.

Result : Mean (N = 3) pKa value was 6.71 (SD = 0.0469) at 20°C

Remark : The results indicate that dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (approximately 1.2).

Reliability : [1] Reliable without restriction.

Reference : Lezotte, F.J. and W.B. Nixon, 2002. Determination of the dissociation constant of barium stearate, Wildlife International, Ltd. Study No. 534C-112, conducted for the Metal Carboxylates Coalition.

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration :
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :

Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculum :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %
%
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result : **Supporting data for dissociation products:**
Acid: Stearate is readily biodegradable: 72% in 28 days (Appendix 1).
Remark :
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Acid:** 48-h LC50 for *C. carpio* > 1000 mg/L; NOEC ≥ 1000 mg/L (Appendix 1). **Metal:** The acute toxicity of barium chloride has been tested in several fish species. Expressed in terms of the metal only, LC50 values ranged from 150 mg Ba/L for a 48-hr test with the brown trout (*Salmo trutta*) to 1,080 mg Ba/L for a 96-hr test with the western mosquitofish (*Gambusia affinis*). The 96-hr LC50 for the mummichog, *Fundulus heteroclitus*, was >1,000 mg Ba/L. (ECOTOX database)
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:**

Acid: For stearate, 47-h NOEC for *Daphnia magna* ≥ 0.09 mg/L (solubility limit) (Appendix 1).

Metal: The acute toxicity of barium chloride has been tested in several invertebrate species. Expressed in terms of the metal only, LC50 values ranged from 46 and 78 mg Ba/L for 96-hr tests with two crayfish, *Orconectes limosus* and *Austropotamobius palliipes pall*, to 238 mg Ba/L for a 96-hr test with the scud, Gammarus pulex. (ECOTOX database)

Reliability :
Reference :

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type :
Guideline/method :
Species :
Endpoint :
Exposure period :
NOEC :
LOEC :
EC0 :
EC10 :
EC50 :
Other :
Other :
Other :
Limit test :
Analytical monitoring :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: For stearate the 72-h EC50 >1016 mg/L for *Scenedesmus subspicatus*; NOEC = 1016 mg/L (Appendix 1).

Metal: The acute toxicity of barium chloride has been tested with the duckweed, *Lemna minor*. The 96-hr EC50 for growth for this species was 25 mg Ba/L. (ECOTOX database)

Reliability :
Reference :

4.4 CHRONIC TOXICITY TO FISH

Type :
Guideline/method :
Species :
Exposure period :
NOEC :
LOEC :
LC0 :
LC50 :
LC100 :

Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	The chronic toxicity of barium chloride has been established with embryo-larval stages of the rainbow trout, *Onchorhynchus mykiss*. The 28-day LC50 in this test was 42.7 mg Ba/L. (ECOTOX database)
Reliability	:	
Reference	:	

4.5 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LOEC	:	
EC0	:	
EC50	:	
EC100	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	The chronic toxicity of barium chloride has been determined in a 21-day study with the water flea *Daphnia magna*. The EC50 for reproduction in this test was 8.9 mg Ba/L. (ECOTOX database)
Reliability	:	
Reference	:	

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vtro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** A wide range of absorption efficiencies has been reported for barium in animal studies. The range of reported oral absorption factors for all animal studies is 0.7% to 85.0%; however, many of the studies determined absorption by a method that does not account for barium that is absorbed and then excreted in the feces, a route that is significant for barium. In general, the presence of food in the gastrointestinal tract appears to decrease barium absorption, and barium absorption appears to be higher in young animals compared to older ones. Studies with several different barium compounds indicate that soluble barium compounds (e.g., barium chloride) and/or barium compounds that yield a dissociated barium ion in the acid environment of the upper gastrointestinal tract (i.e., barium chloride and barium sulfate) have similar absorption efficiencies. Once absorbed, the highest concentrations of barium are found in the bone (91% of total body burden). The feces is the primary route of excretion, accounting for 90% of more of the total eliminated. (Information from U.S. EPA 1999, Toxicological Review of Barium and Compounds)
Reliability	:	
Reference	:	

5.1.1 ACUTE ORAL TOXICITY

Type	:	
Guideline/Method	:	
Species	:	Rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
LD50	:	9820 mg/kg
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Acid:** Rat LD50 > 2000 mg/kg bw for stearate(Appendix 1). **Metal:** Male rats (5 males per treatment) were dosed with 0.464 to 10.0 g/kg of euectic (triple pressed) stearic acid. The LD50 was reported as >10.0 g/kg. Reference: Cosmetic, Toiletries, and Fragrence Association (1987) Cosmetic Ingredient Review, Final Report on the Safety Assessment of Olielc Acid, Lauric Acid, Palmitic Acid, Myristic Acid and Stearic Acid. J. Am. Coll. Toxicol. Vol. 6, No. 3, pp321-401. (Subsequently refered to as CTFA#3.). The acute oral LD50 for barium chloride in the rat is 118 mg/kg (equivalent to 77.8 mg Ba/kg). (World Health Organization, 1990, Environmental Health Criteria 107 Barium)
Reliability	:	[4] Reliability Unknown, insufficient information
Reference	:	Shepard MSDS

5.1.2 ACUTE INHALATION TOXICITY

Type	:	
Guideline/method	:	
Species	:	
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	
LC50	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

5.1.3 ACUTE DERMAL TOXICITY

Type	:	

Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Stearic acid, 10-100 mM in olive oil was dosed intradermally in guinea pigs and rabbits which resulted in mild erythema and slight induration of skin. CTFA#3 ref 157. Stearic acid as a 20% formulations was applied at 2.0 ml/kg of product to abraded/intact sites on the backs of rabbits. After four weeks no mortaltities and slight edema and sesqumation were observed. CTFA#3 ref 163.
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Metal: In rabbits, barium nitrate causes mild skin irritation after a 24-hr exposure. (World Health Organization, 1990, Environmental Health Criteria 107 Barium)
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :

Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result : **Supporting information for dissociation products:**
Acid: Stearic acid (eutatectic, commercial grade) applied to the eyes of albino rabbits following the Draise method. Results ranged from no irritation to mild conjunctival eryhtema in 2 rabbits subsiding by 72 hours. Stearic acid in various formulations at lower strengths showed similar results (CTFA#3).

Metal: In rabbits, barium nitrate causes severe eye irritation after a 24-hr exposure. (World Health Organization, 1990, Environmental Health Criteria 107 Barium)
Remark :
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: LOAEL was 3000 ppm based on mortality. (Appendix 1). Chronic feeding studies with rats exposed to stearic acid have shown reversible effects with no significant pathological lesions. Animals fed for 24 weeks with stearic acid (50g/kg/day) developed foreign body type reaction in perigenital fat. Lipogranulomas were oberved to be reversible. Rats fed

perigenital fat. Lipogranulomas were oberved to be reversible. Rats fed stearic acid (3000 ppm) for 30 weeks developed anorexia, severe pulmonary infection, high mortality. No significant pathological lesions were observed. (CTFA#3 ref 151,152., Appendix 1).

Metal: Several subchronic and chronic toxicity studies have been conducted on barium compounds in rats and mice. These studies provide evidence that the kidney, including glomerular damage, is a sensitive target of barium toxicity in rats and mice fed a nutritionally adequate diet (U.S. EPA 1999, Toxicological Review of Barium and Compounds). Hypertension has also been observed in studies in which rats were fed a marginally adequate diet, particularly one with inadequate calcium levels. Hypertension has been observed in humans who ingested high doses of barium compounds under occupational exposure conditions, but has not been observed in longer term human studies following oral exposure to lower concentrations of barium in drinking water (U.S. EPA 1999, Toxicological Review of Barium and Compounds).

The most significant repeated-dose study on barium exposed rats and mice to barium chloride dihydrate via drinking water (0, 500, 1250, or 2500 ppm) for approximately 2 years (NTP, 1994). For mice, the authors estimated the daily doses as 30, 75, and 160 mg Ba/kg-day for males, and 40, 90, and 200 mg Ba/kg-day for females. For rats, the estimated daily doses were 15, 30, and 60 mg Ba/kg-day for males, and 15, 45, and 75 mg Ba/kg-day for females. For the 2,500 ppm exposure group, survival rates for mice, but not for rats, were significantly decreased compared to controls. Nephropathy and other kidney effects were also observed in mice receiving the highest barium exposure; however, no chemical-related kidney lesions were observed in any of the rat treatment groups. The only potential sign of renal toxicity was an increase in relative kidney weight in female rats at 2,500 ppm. Based on these results, 75 mg Ba/kg-day was designated a chronic LOAEL and 45 mg Ba/kg-day a chronic LOAEL for female rats for renal effects in the NTP (1994) study. [Reference: National Toxicology Program (NTP). 1994. NTP Technical report on the toxicology and carcinogenesis studies of barium chloride dihydrate (CAS No. 10326-27-9) in F344/N rats and B6C3F1 mice (drinking water studies). NTP TR 432. Research Triangle Park. NIH Pub. No. 94-3163. NTIS no. PB94-214178.]

Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :
Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :

Result :

Remark : **Supporting information for dissociation products:**
Acid: Not mutagenic in *S. typhimurium* with and without metabolic activation (Appendix 1). Stearic acid was tested for mutagenicity using the Ames test with *Salmonella typhumurium* strains TA98, TA100, TA1535, TA1537, TA1538. Spot tests were performed using 50 mg/ml Stearic acid suspensions in the distilled waster (50 µg/plate) with and without microsomal activation from hepatic S9 fractions from rats induced with Aroclor 1254 (50 µg/plate). Positive controls were 2-aminoanthracene and 4-nitro—o-phenylenediamine in dimethyl sulfoxide, 9-aminoacridinein ethanol, and sodium azide in distilled water with and without metabolic activation. (CTFA#3.)
Metal: Most in vitro studies have found that barium chloride and barium nitrate did not induce gene mutations in bacterial assays with or without metabolic activation (in U.S. EPA 1999, Toxicological Review of Barium and Compounds). Ames assays with *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA97, TA98, and TA100 with or without metabolic activation (Monaco et al., 1990, 1991; NTP, 1994), rec assays with *Bacillus subtilis* strains H17 and H45 (Nishioka, 1975; Kanematsu et al., 1980), and a microscreen assay with *Escherichia coli* (Rossman et al., 1991) with metabolic activation have produced negative results with barium chloride. Negative results have also been observed for barium nitrate in the rec assay with *B. subtilis* strains H17 and H45 (Kanematsu et al., 1980). Barium chloride induced gene mutations in L5178Y mouse lymphoma cells with metabolic activation but not in the absence of metabolic activation (NTP, 1994). Neither barium acetate or barium chloride decreased the fidelity of DNA synthesis in avian myeleblastosis virus DNA polymerase (Sirover and Loeb, 1976). In mammalian cells, barium chloride did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells, with or without activation (NTP, 1994). (Note: All citations in this section are “as cited in” U.S. EPA 1999, Toxicological Review of Barium and Compounds)

Reliability :

Reference :

5.6 GENETIC TOXICITY ‘IN VIVO‘

Type :

Guideline/method :

Species :

Strain :

Sex :

Route of admin. :

Exposure period :

Doses :

Year :

GLP :

Test substance :

Method :

Method detail :

Result :

Remark :

Reliability :

Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type	:
Guideline/method	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Duration of test	:
Doses	:
Control group	:
NOAEL maternal tox.	:
NOAEL teratogen.	:
Other	:
Other	:
Other	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:
Remark	: **Supporting information for dissociation products:** **Metal:** A subchronic single-generation reproductive/developmental toxicity study did not find any significant alterations in gestational length, pup survival, or occurrence of external abnormalities in rats and mice exposed to barium chloride in drinking water at levels up to 2,000 ppm (Dietz et al., 1992 as cited in U.S. EPA 1999, Toxicological Review of Barium and Compounds). This study also did not find any significant alterations in reproductive endpoints in the Fo rats and mice; however, the low pregnancy rates in all groups, including controls, limit the usefulness of this study for determining an LOAEL.
Reliability	:
Reference	:

5.8.3 TOXICITY TO REPRODUCTION

Type	:
Guideline/method	:
In vitro/in vivo	:
Species	:
Strain	:
Sex	:
Route of admin.	:
Exposure period	:
Frequency of treatment	:
Duration of test	:
Doses	:
Control group	:
Year	:
GLP	:
Test substance	:
Method	:

Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Metal: A subchronic single-generation reproductive/developmental toxicity study did not find any significant alterations in gestational length, pup survival, or occurrence of external abnormalities in rats and mice exposed to barium chloride in drinking water at levels up to 2,000 ppm (Dietz et al., 1992 as cited in U.S. EPA 1999, Toxicological Review of Barium and Compounds). This study also did not find any significant alterations in reproductive endpoints in the Fo rats and mice; however, the low pregnancy rates in all groups, including controls, limit the usefulness of this study for determining an LOAEL.
Reliability :
Reference :

24.0 OTHER INFORMATION

24.1 CARCINOGENICITY

Supporting information for dissociation products:
Metal: A weight-of-evidence evaluation and cancer characterization has been performed for barium compounds in the Toxicological Review of Barium and Compounds conducted in support of summary information on the Integrated Risk Information System (IRIS)(U.S. EPA, 1999). Oral exposure studies in rats and mice did not find significant increases in tumor incidence following chronic exposure to barium compounds for up to two years (NTP, 1994; McCauley et al., 1985; Schroeder and Mitchener, 1975a,b). Inhalation exposure and intratracheal studies conducted by Tarasenko et al. (1977) were judged to be inadequate for carcinogenicity evaluation because of several deficiencies in design and reporting. Based on the available weight of evidence, it was concluded that under EPA's proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996) barium is considered not likely to be carcinogenic to humans following oral exposure and its carcinogenic potential cannot be determined following inhalation exposure. (Note: All citations in this section are "as cited in" U.S. EPA 1999, Toxicological Review of Barium and Compounds)

1.0 SUBSTANCE INFORMATION

Generic Name	:	Aluminum Tristearate
Chemical Name	:	
CAS Registry No.	:	673-12-7
Component CAS Nos.	:	
EINECS No.	:	
Structural Formula	:	$Al(C_{18}H_{35}O_2)_2$

Molecular Weight	:	877.35
Synonyms and Trade names	:	Alugel 34TN; Aluminum Stearate; Aluminum Stearate (1:3); Metasap XX; Monoaluminum Stearate; Octadecanoic Acid, Aluminum Salt; ROFOB 3; Stearic Acid, Aluminum Salt.
References	:	Cosmetic, Toiletry and Fragrance Association (1982) Final Report of the Safety Assessment of Lithium Stearate, Aluminum Stearate, Aluminum Tristearate, Ammonium Stearate, Calcium Stearate, Magnesium Stearate, Potassium Stearate, Sodium Stearate, and Zinc Stearate. J. A. Coll. Toxicol. 1 (2): 143-177. (Subsequently called CTFA #9).

2.1 MELTING POINT

Type	:	
Guideline/method	:	
Value	:	117-120 °C
Decomposition	:	at °C
Sublimation	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: The melting point reported for stearate is 69.7°C (Appendix 1).
Reliability	:	[4] Reliability unknown, insufficient information
Reference	:	HSDB (2002) Hazardous Substances Databank, National Library of Medicine (http://toxnet.nlm.nih.gov)[HSDB/26]

2.2 BOILING POINT

Type	:	
Guideline/method	:	
Value	:	°C at hPa
Decomposition	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: The reported range for stearate is 376-383 °C (Appendix 1).
Reliability	:	
Reference	:	

2.3 DENSITY

Type	:	
Guideline/method	:	
Value	:	1.070
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting data for dissociation products:** **Acid**: Reported value for stearate is 0.9408 at 20°C (HSDB 8/16/02).
Reliability	:	
Reference		HSDB 26

2.4 VAPOR PRESSURE

Type	:	

Guideline/method :
Value : hPa at °C
Decomposition :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: 1.0 hPa at174°C (Appendix 1).
Reliability :
Reference :

2.5 PARTITION COEFFICIENT

Type :
Guideline/method :
Partition coefficient :
Log Pow : at °C
pH value :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Log Kow for stearate is reported as 8.2 at 25°C (Appendix 1).
Reliability :
Reference :

2.6.1 SOLUBILITY IN WATER

Type :
Guideline/method :
Value : Practically insoluble in water
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at °C
Description :
Stable :
Deg. product :
Year :
GLP :
Test substance :
Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: The reported values for stearate are 0.60 mg/L at 25 °C and 2.9 mg/L at 25 °C (Appendix 1).
Reliability :

Reference :

2.7 FLASH POINT

Type :
Guideline/method :
Value : °C
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.1.1 PHOTODEGRADATION

Type		
Guideline/method	:	
Light source	:	
Light spectrum	:	
Relative intensity	:	based on
Spectrum of substance	:	lambda (max, >295nm) :
		epsilon (max) :
		epsilon (295) :
Conc. of substance	:	at °C
DIRECT PHOTOLYSIS		
Half-life (t1/2)	:	
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	
Conc. of sensitizer	:	
Rate constant	:	
Degradation	:	
Deg. product	:	
Year	:	
GLP	:	
Test substance	:	
Deg. products CAS#	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	
Reliability	:	
Reference	:	

3.1.2 DISSOCIATION

Type	:	
Guideline/method	:	
pKa	:	
Year	:	
GLP	:	
Test substance	:	
Approximate water solubility	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	Dissociation could not be evaluated for this compound due to the low solubility.
Reliability	:	
Reference	:	
Type	:	
Guideline/method	:	
pKa	:	

Reference :

3.2.1 MONITORING DATA

Type of measurement :
Media :
Concentration :
Substance measured :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.3.1 TRANSPORT (FUGACITY)

Type :
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Year :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

3.5 BIODEGRADATION

Type :
Guideline/method :
Inoculums :
Concentration : related to
related to
Contact time :
Degradation : (±) % after day(s)
Result :
Kinetic of test subst. : % (specify time and % degradation)
%
%
%
%
Control substance :
Kinetic : %
%
Deg. product :
Year :
GLP :
Test substance :

Deg. products CAS# :
Method :
Method detail :
Result :
Remark : **Supporting data for dissociation products:**
Acid: Stearate is readily biodegradable: 72% in 28 days (Appendix 1)
Reliability :
Reference :

3.7 BIOCONCENTRATION

Type :
Guideline/method :
Species :
Exposure period : at °C
Concentration :
BCF :
Elimination :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

4.1 ACUTE TOXICITY TO FISH

Type	:	
Guideline/method	:	
Species	:	
Exposure period	:	
NOEC	:	
LC0	:	
LC50	:	
LC100	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Acid:** 48-h LC50 for *C. carpio* > 1000 mg/L; NOEC ≥ 1000 mg/L (Appendix 1). **Metal:** For a test with aluminum chloride, the 96-hr LC50 was 27.1 mg Al/L for *Gambusia affinis* (mosquitofish) (Reference 508 in the ECOTOX database). For a test with aluminum chloride, the 48-hr LC50 was 80 mg Al/L for *Danio rerio* (zebrafish) (Reference 11199 in the ECOTOX database). For a test with aluminum chloride, the 96-hr LC50 was 8.6 mg Al/L for *Oncorhynchus mykiss* (rainbow trout) (Reference 3689 in the ECOTOX database).
Reliability	:	
Reference	:	

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:
Guideline/method	:
Species	:
Exposure period	:
NOEC	:
EC0	:
EC50	:
EC100	:
Other	:
Other	:
Other	:
Limit test	:
Analytical monitoring	:
Year	:
GLP	:
Test substance	:
Method	:
Method detail	:
Result	:

Remark	:	**Supporting information for dissociation products:** **Acid:** For stearate the 48-h NOEC for *Daphnia magna* $\geq$ 0.09 mg/L (solubility limit) (Appendix 1). **Metal:** For aluminum chloride, the 48-hr EC50 for *Daphnia magna* ranged from 3.9 to 27.3 mg Al/L in three different tests (IUCLID, 2000). The 48-hr LC0 for the eastern oyster, *Crassotrea virginica*, was 7.5 mg Al/L (IUCLID, 2000). The most sensitive invertebrate to aluminum chloride is the marine worm *Ctenodrillus serratus* with a 96-hr LC50 of 0.097 mg Al/L (Reference 2146 in the ECOTOX database).
Reliability	:	
Reference	:	

4.3 TOXICITY TO AQUATIC PLANTS (E.G., ALGAE)

Type	:	
Guideline/method	:	
Species	:	
Endpoint	:	
Exposure period	:	
NOEC	:	
LOEC	:	
EC0	:	
EC10	:	
EC50	:	
Other	:	
Other	:	
Other	:	
Limit test	:	
Analytical monitoring	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Acid:** For stearate the 72-h EC50 >1016 mg/L for (*Scenedesmus subspicatus*; NOEC = 1016 mg/L (Appendix 1). **Metal:** Effects on the algae *Scenedesmus quadricauda* are seen at levels of 1.5 to 2.0 mg Al/L in 4-day tests with aluminum chloride (IUCLID, 2000). Effects on the population growth of *Chlorella vulgaris* were seen at a level of 0.225 mg/L in a 4-month study with aluminum chloride (IUCLID, 2000).
Reliability	:	
Reference	:	

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In vitro/in vivo	:	
Type	:	
Guideline/method	:	
Species	:	
Number of animals	:	
Males	:	
Females	:	
Doses	:	
Males	:	
Females	:	
Vehicle	:	
Route of administration	:	
Exposure time	:	
Product type guidance	:	
Decision on results on Acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2nd: 3rd:
Toxic behavior	:	
Deg. product	:	
Deg. products CAS#	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** Aluminum is poorly absorbed following either oral or inhalation exposure and is essentially not absorbed dermally. Approximately 0.1% of ingested aluminum is usually absorbed, although absorption of the more bioavailable forms can be on the order of 1%. The unabsorbed aluminum is excreted in the feces. The 10-fold range in absorption of aluminum is due to differences in bioavailability related to the form of ingested aluminum (type of anion) and the presence of dietary constituents which can complex with aluminum and thereby enhance or inhibit its absorption. In acidic conditions such as the stomach (pH»2) aluminum occurs primarily as a monomolecular hexahydrate, Al(H20)6+3, which is generally abbreviated as Al+3 and referred to as “free” aluminum. As pH increases, a series of aluminum hydroxy complexes are formed by successive deprotonation so that, in near neutral conditions such as the intestines, the predominant form is aluminum hydroxide, Al(OH)3, an insoluble precipitate. The acidic conditions and mixing/residence time in the stomach appear to ensure that the majority of consumed aluminum will be solubilized to monomolecular aluminum (most likely free Al+3), regardless of the compound and form (e.g., food, drinking water, antacid tablets) in which it was ingested. The solubilized aluminum that is in the stomach can recomplex with the anion from the original aluminum compound that was ingested or form new complexes with dietary ligands. The dietary ligands that appear to play an

important role in the complexation process include simple mono-, di-, and tricarboxylic acids (particularly citric acid). The vast majority of desolubilized aluminum is not complexed, is rapidly precipitated as insoluble (unabsorbable) aluminum hydroxide in the duodenum by the near–neutral pH conditions, and is ultimately excreted in the feces. (Text from Agency for Toxic Substances and Disease Registry [ATSDR] 1999, Toxicological Profile for Aluminum)

Reliability :
Reference :

5.1.1 ACUTE ORAL TOXICITY

Type :
Guideline/Method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Rat LD50 > 2000 mg/kg bw for stearate(Appendix 1).Male rats (5 males per treatment) were dosed with 0.464 to 10.0 g/kg of eutectic (triple pressed) stearic acid. The LD50 was reported as >10.0 g/kg.
Reference: Cosmetic, Toiletries, and Fragrance Association (1987) Cosmetic Ingredient Review, Final Report on the Safety Assessment of Oleic Acid, Lauric Acid, Palmitic Acid, Myristic Acid and Stearic Acid. J. Am. Coll. Toxicol. Vol. 6, No. 3, pp321-401. (Subsequently referred to as CTFA#3.)
Metal: The rat oral LD50 for aluminum chloride has been reported to range from 380 to 3,730 mg/kg bw, with several values in the 3,300 to 3,700 mg/kg bw range. Mouse LD50 values for aluminum chloride range from 770 to 3,805 mg/kg bw. (IUCLID, 2000)
Reliability :
Reference :

5.1.2 ACUTE INHALATION TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time :
LC50 :

Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark :
Reliability :
Reference :

5.1.3 ACUTE DERMAL TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
LD50 :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Stearic acid, 10-100 mM in olive oil was dosed intradermally in guinea pigs and rabbits which resulted in mild erythema and slight induration of skin. CTFA#3 ref 157. Stearic acid as a 20% formulations was applied at 2.0 ml/kg of product to abraded/intact sites on the backs of rabbits. After four weeks no mortalities and slight edema and sesqumation were observed. CTFA#3 ref 163.
Reliability :
Reference :

5.2.1 SKIN IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :

Result :
Remark : **Supporting information for dissociation products:**
Metal: Solutions of 2.5 to 5.0 % aluminum chloride hexahydrate are mildly to moderately irritating to human skin when applied once daily for 3 days. (IUCLID, 2000)
Reliability :
Reference :

5.2.2 EYE IRRITATION

Type :
Guideline/method :
Species :
Strain :
Sex :
Concentration :
Dose :
Exposure time :
Number of animals :
Vehicle :
Classification :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Stearic acid (eutatectic, commercial grade) applied to the eyes of albino rabbits following the Draise method. Results ranged from no irritation to mild conjunctival erythema in 2 rabbits subsiding by 72 hours. Stearic acid in various formulations at lower strengths showed similar results (CTFA#3).
Reliability :
Reference :

5.4 REPEATED DOSE TOXICITY

Type :
Guideline/method :
Species :
Strain :
Sex :
Number of animals :
Route of admin. :
Exposure period :
Frequency of treatment :
Post exposure period :
Doses :
Control group :
NOAEL :
LOAEL :
Other :
Year :
GLP :

Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: LOAEL was 3000 ppm based on mortality. (Appendix 1). Chronic feeding studies with rats exposed to stearic acid have shown reversible effects with no significant pathological lesions. Animals fed for 24 weeks with stearic acid (50g/kg/day) developed foreign body type reaction in perigenital fat. Lipogranulomas were observed to be reversible. Rats fed stearic acid (3000 ppm) for 30 weeks developed anorexia, severe pulmonary infection, high mortality. No significant pathological lesions were observed. (CTFA#3 ref 151,152., Appendix 1).

Metal: For aluminum compounds, neurotoxicity is the most sensitive endpoint that has been identified in repeated dose toxicity studies (ATSDR 1999, Toxicological Profile for Aluminum). Neurobehavioral impairments have been identified in orally exposed adults, as well as weanlings and young animals exposed by several different routes (e.g., gestation, lactation, ingestion, and combinations thereof). The most frequently observed behaviors in adult mice (the most sensitive species) include decreases in motor activity, grip strength, and startle responsiveness. In weanlings and young mice, the most common effects are increases in grip strength and landing foot splay, and decreased thermal sensitivity. The Minimum Risk Level (MRL) for aluminum derived by the Agency for Toxic Substances and Disease Registry (ATSDR) is based on a NOAEL of 62 mg Al/kg/day determined in a study by Golub et al. (1989) with adult mice exposed to dietary aluminum lactate for 6 weeks (ATSDR 1999, Toxicological Profile for Aluminum). The LOAEL in this study was 130 mg Al/kg/day based on decreased spontaneous motor activity.
Reliability :
Reference :

5.5 GENETIC TOXICITY 'IN VITRO'

Type :
Guideline/method :
System of testing :
Species :
Strain :
Test concentrations :
Cytotoxic concentr. :
Metabolic activation :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Acid: Not mutagenic in *S. typhimurium* with and without metabolic activation (Appendix 1). Stearic acid was tested for mutagenicity using the Ames test with *Salmonella typhumurium* strains TA98, TA100, TA1535, TA1537, TA1538. Spot tests were performed suing 50 mg/ml Stearic acid suspensions in the distilled waster (50 µg/plate) with and without microsomal activation from hepatic S9 fractions from rats induced with

microsomal activation from hepatic S9 fractions from rats induced with Aroclor 1254 (50 µg/plate). Positive controls were 2-aminoanthracene and 4-nitro—o-phenylenediamine in dimethyl sulfoxide, 9-aminoacridinein ethanol, and sodium azide in distilled water with and without metabolic activation. (CTFA#3.)

Metal: It appears that aluminum can cause genotoxicity under some circumstances, although most study data indicate that aluminum does not directly interact with DNA in mutagenicity tests (ATSDR 1999, Toxicological Profile for Aluminum). Negative mutagenicity data come from transformation assays in Syrian hamster cells (DiPaola and Casto, 1979), recombination repair assays in *Bacillus subtilis* (Kanematsu et al., 1980), and Ames assays with Salmonella typhimurium (Marzin and Phi, 1985). Genotoxicity has been demonstrated in an in vitro study that showed aluminum chloride to cause cross-linking of chromosomal proteins and DNA in ascites hepatoma cells from Sprague-Dawley rats (Wedrychowski et al., 1986). Micromolar aluminum concentrations have also been shown to reduce 3H-thymidine incorporation in a transformed cell line (Blair et al., 1989), suggesting that aluminum may impede cell cycle progression; however, the results have not been verified in normal, untransformed cells. [Note: all citations are from ATSDR 1999, Toxicological Profile for Aluminum.]

Reliability :
Reference :

5.6 GENETIC TOXICITY 'IN VIVO'

Type :
Guideline/method :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Doses :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Metal: Data from an in vivo study with mice indicate that aluminum chloride is clastogenic when dosed via an intraperitoneal injection, causing an increase in chromatid-type aberrations in bone marrow cells (Manna and Das 1972 as cited in ATSDR 1999, Toxicological Profile for Aluminum). Although no dose-response relationship was found in this study, the highest dose of aluminum chloride did produce the greatest number of aberrations.
Reliability :
Reference :

5.8.2 DEVELOPMENTAL TOXICITY

Type :
Guideline/method :

Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
NOAEL maternal tox. :
NOAEL teratogen. :
Other :
Other :
Other :
Year :
GLP :
Test substance :
Method :
Method detail :
Result :
Remark : **Supporting information for dissociation products:**
Metal: Developmental toxicity studies in animals have shown that oral exposure to aluminum induced skeletal variations such as delayed ossification in rats and mice under conditions that enhance its uptake, particularly maternal intake of compounds that are highly bioavailable (e.g., aluminum citrate and nitrate), concurrent exposure to dietary constituents that contribute to increased absorption of aluminum (e.g., citrate), and/or bolus administration by gavage (ATSDR 1999, Toxicological Profile for Aluminum). Given the relatively high bioavailability of the developmentally toxic forms of aluminum and bolus administration, it is possible that the skeletal changes are consequent to phosphate depletion caused by excess binding with aluminum in the maternal gut. Neurobehavioral deficits have been observed on oral studies with weanlings and young developing mice and rats exposed to aluminum by gestation, combined gestation and lactation, combined gestation and lactation followed by postweanling ingestion, and postweanling ingestion alone. The most frequently affected behaviors in exposed weanlings and young animals included increases in grip strength and landing foot splay, decreased thermal sensitivity, and negative geotaxis. Teratogenic changes have not been associated with gestational exposure to aluminum. (Text from ATSDR, 1999, Toxicological Profile for Aluminum)
Reliability :
Reference :

5.8.3 TOXICITY TO REPRODUCTION

Type :
Guideline/method :
In vitro/in vivo :
Species :
Strain :
Sex :
Route of admin. :
Exposure period :
Frequency of treatment :

Duration of test	:	
Doses	:	
Control group	:	
Year	:	
GLP	:	
Test substance	:	
Method	:	
Method detail	:	
Result	:	
Remark	:	**Supporting information for dissociation products:** **Metal:** Oral studies in male and female animals show some inconsistencies, but generally indicate that reproductive toxicity is not an effect of concern for aluminum-exposed people (ATSDR 1999, Toxicological Profile for Aluminum). Mating success (numbers of litters and offspring) was not affected in a three-generation study with Dobra voda mice that were exposed to 49 mg Al/kg/day in drinking water and base diet over a period of 180 to 390 days (Ondriecka et al., 1966). No reproductive effects were observed in pregnant Swiss Webster mice that consumed 250 mg al/kg/day as aluminum lactate throughout gestation and lactation (Golub et al., 1992a). An increased incidence of resorptions occurred in mice that were gestationally exposed to aluminum chloride by gavage (Crammer et al., 1986), but no reproductive effects were found in rats similarly exposed to aluminum chloride, hydroxide, or citrate (Gomez et al., 1991; Miswa and Shigeta, 1992). [Note: all citations are from ATSDR 1999, Toxicological Profile for Aluminum.]
Reliability	:	
Reference	:	

25.0 OTHER INFORMATION

25.1 Carcinogenicity

Supporting information for dissociation products:
Metal: Aluminum and aluminum compounds are not known to cause cancer in humans. Although some workers in the aluminum industry have had a higher than expected cancer mortality rate, all indications are that this is due to pitch fume or other carcinogens to which they are exposed, and not due to the presence of aluminum compounds (IARC, 1984). There are several cancer studies on animals in the scientific literature. None of these studies show that aluminum is carcinogenic (Hackenberg 1972; Oneda et al 1994; Pigott et al 1981; Schroeder and Mitchener 1975a, 1975b). [Note: all citations are from ATSDR 1999, Toxicological Profile for Aluminum.]

6.2 Skin Sensitization

Supporting information for dissociation products:
Metal: Aluminum chloride has not been shown to cause skin sensitization in the guinea pig using either the Buehler test or the Maximization test, or in the mouse using the Ear Swelling Test (IUCLID, 2000).