I U C L I D

Data Set

Existing Chemical	:	ID: 301-10-0
CAS No.	:	301-10-0
EINECS Name	:	tin bis(2-ethylhexanoate)
EC No.	:	206-108-6
Molecular Formula	:	C8H16O2.1/2Sn
Producer related part		
Company	:	Parametrix Inc.
Creation date	:	02.10.2003
Substance related part		
Company	:	Parametrix Inc.
Creation date	:	02.10.2003
Status	:	
Memo	:	
Printing date	:	20.11.2003
Revision date	:	
Date of last update	:	20.11.2003
Number of pages	:	29
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1. General Information

Id 301-10-0
Date 20.11.2003

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	O=C(O[Sn]OC(=O)C(CC)CCCC)C(CC)CCCC
Molecular formula	:	C16H30O4Sn
Molecular weight	:	405.1 g/mol
Petrol class	:	

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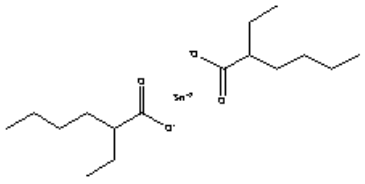
1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	inorganic
Physical status	:	liquid
Purity	:	ca. 60 - 100 % v/v
Colour	:	
Odour	:	

Attached document : Structual diagram as bitmap figure.



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1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2-Ethylhexanoic acid, tin(II) salt

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Bis(2-ethylhexanoate)tin

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Ethylhexanoic acid tin(2+) salt

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Hexanoic acid, 2-ethyl, tin salt

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Hexanoic acid, 2-ethyl-, tin(2+) salt

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Stannous ethylhexanoate

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Stannous octoate

06.10.2003

Stannous-2-ethyl hexanoate

06.10.2003

Tin 2-ethylhexanoate

06.10.2003

Tin II octoate

06.10.2003

Tin(II) 2-ethylhexanoate

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Tin(II) bis(2-ethylhexanoate)

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Tin(II) ethylhexanoate

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1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value	:	< 45 °C
Sublimation	:	
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS
Remark	:	Reported as Freezing Point: <113 deg. F.
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]

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2.2 BOILING POINT

2.3 DENSITY

Type	:	density
Value	:	= 1.25 g/cm³ at °C
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS
Remark	:	Reported as Specific Gravity (g/mL): 1.25.
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]

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2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= 2.67 at °C
pH value	:	
Method	:	other (measured): not reported
Year	:	
GLP	:	no data
Test substance	:	other TS
Remark	:	Reported as Log Kow: 2.67.
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]

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2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	ca. 100 mg/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	moderately soluble (100-1000 mg/L)
Stable	:	
Deg. product	:	
Method	:	other: determined visually
Year	:	
GLP	:	yes
Test substance	:	other TS
Remark	:	Preliminary work conducted as part of GLP study to determine the dissociation constant of the test substance in water at 20°C. Increasing volumes of NANOpure water were added to a known amount of test substance. Solubility was defined as the point where the test substance could no longer be determined visually. Solubility of the test substance was determined to be approximately 100 mg/l.
Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]; hazy yellow liquid, 95% purity, source: Aldrich Chemical Company.
Reliability	:	(4) not assignable Documentation insufficient for assessment - provided for information only. Preliminary study with subjective determination.

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2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	> 142 °C
Type	:	
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS
Remark	:	Reported as Flashpoint: >287 deg. F (PMCC)
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]

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2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant	:	pKa = 5.09 at 20°C
Method	:	other: OECD Guide-line 112, "Dissociation Constants in Water" (1981) and OPPTS 830.7370, "Dissociation Constants in Water" (1996)
Year	:	
GLP	:	yes
Test substance	:	other TS
Method	:	The approximate water solubility of the test substance (as determined visually in a preliminary study) was 100 mg/L. A preliminary study was conducted to determine the approximate equivalence point. In the definitive study, three replicate samples of stannous 2-ethylhexanoate were each prepared at a nominal concentration of 50 mg/L by fortification of degassed water (NANOpure - ASTM Type II) with a 10 mg/mL stock solution of the test substance in methanol. Each sample was titrated against 0.001 N sodium hydroxide while maintained at a test temperature of 20 ± 1°C. At least 10 incremental additions were made prior to reaching 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 (purity 85.0 %) and 4-nitrophenol (purity 100.5 %) were used as reference substances. Samples of the reference substances were prepared at 0.01 M and underwent the same test procedure as the test substance, in order to verify the calibration of the procedure.
Result	:	The pKa value for phosphoric acid were 2.52 and 7.10 at 20 deg. C. The pKa value for 4-nitrophenol was 7.16. The pKa values for the reference substances were in good agreement with published literature values. The mean (n = 3) pKa value for tin (II) ethylhexanoate was determined to be 5.09 (SD = 0.0337, CV - 0.662%) at 20°C. These results indicate that dissociation of the test substance will occur at both environmentally-relevant (i.e., approximately neutral) and physiologically-relevant (i.e., approximately 1.2) pH values.
Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]; hazy yellow liquid, 95% purity, source: Aldrich Chemical Company.
Reliability	:	(1) valid without restriction Guideline study conducted under GLP.

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2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male
Number of animals	:	5
Vehicle	:	other: none
Doses	:	1.6, 3.2, 6.4 and 12.8 g/kg
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method : Test animals had initial body weights ranging from 200-250g and were fasted 24 hours prior to dosing. Animals were caged in groups of 5 and maintained at a temperature of 72 ± 2 deg. F (22.2 ± 2 deg. C), under an 8-hour light/16-hour dark photoperiod. Food and water were provided ad libitum, except during the pre-dosing fasting period.

The test material was administered as supplied at concentrations of 1.6, 3.2, 6.4, and 12.8 g/kg, via intragastric intubation, to four groups of 5 male rats. Animals were observed for 21-days post-exposure and mortalities were recorded daily. The LD50 was calculated using the Thompson Moving Average Method.

Result : Mortality (number of dead/total number tested), by dose level tested:
1.6 g/kg: 0/5
3.2 g/kg: 1/5
6.4 g/kg: 3/5
12.8 g/kg: 4/5

Animals in the 6.4 and 12.8 g/kg dose groups were observed to be listless following test material administration. Mortalities in these two dose groups occurred within the first four days following test substance administration. The single mortality in the 3.2 g/kg dose group occurred on day 12.

The oral LD50 (+95% confidence limits) of the test substance was reported as 5.87 (3.14-10.98) g/kg.

Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]
Reliability	:	(2) valid with restrictions Very brief description of methods and results. Characterization of test material was not reported. No pathological examinations of the test animals were reported.

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Type	:	LD50
Value	:	= 3400 mg/kg bw
Species	:	rat
Strain	:	

Sex	:	male
Number of animals	:	6
Vehicle	:	other: paraffin oil
Doses	:	1.0, 1.7, 2.89, 4.91, and 8.35 g/kg bw
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS

Method : Groups of 6 male rats were exposed to the test substance at dose levels of 1.0, 1.7, 2.89, 4.91, and 8.35 g/kg bw. The test material was administered in paraffin oil as a single dose by oral gavage. The dose volume was 10 ml/kg. Animals were observed animals for 14 days post-exposure and mortalities were recorded. The LD50 was calculated using the Thompson Moving Average Method. At the end of the observation period, surviving animals were sacrificed and all animals underwent gross pathological examination.

Result : Mortality (number of animals dead/total number tested), by dose level:
1.0 g/kg bw: 0/6
1.7 g/kg bw: 0/6
2.89 g/kg bw: 3/6
4.91 g/kg bw: 4/6
8.35 g/kg bw: 6/6

All mortalities occurred within 1 to 2 days after dosing. Clinical signs of toxicity included piloerection, soiled coat, hypokinesis and ataxia. No clinical signs persisted after 11 days post-exposure. Postmortem observations revealed fluid gut contents, pale kidneys, mottled liver, and patchy pink lung.

The oral LD50 (+95% confidence limits) of the test substance was reported as 3.4 (2.5-4.8) g/kg bw.

Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]
Reliability	:	(2) valid with restrictions Characterization of test material was not reported. No information on body weight changes, preparation of dosing solution, and housing and feeding conditions.

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Type	:	LD50
Value	:	> 5000 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: olive oil
Doses	:	500, 1000, 3000 mg/kg bw (2 animals); 5000 mg/kg bw (10 animals)
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method : Stannous octoate was administered in olive oil by gavage to groups of 2 or 10 rats. Control animals received olive oil only. Animals were observed for 10 days, then sacrificed and examined for gross and microscopic abnormalities.

Result	:	Mortality (number of dead/total number tested), by dose level tested: 500 mg/kg: 0/2 1000 mg/kg: 0/2 3000 mg/kg: 0/2 5000 mg/kg: 1/10 (death occurred <16-h post-administration) All animals had diarrhea and slight body weight loss. Microscopic abnormalities observed, by dose level tested: 500 mg/kg: hyperemic medulla in the kidney. 1000 mg/kg: hyperemic medulla in the kidney, and perilobular vacuolation of cells and hyperemia in the liver. 3000 mg/kg: Hyperemic cortex and medulla and small amount of tubular necrosis and regeneration in the kidney, pronounced perilobular vacuolation of cells and hyperemia in the liver, and generalized lymphatic infiltration in the intestine. 5000 mg/kg: hemorrhages in the corticomedullary zone and some necrotic changes in tubular cells in the kidney, and widespread vacuolation of cells and hyperemia in the liver. Based on the results reported, the LD50 would be expected to be >5000 mg/kg bw.
Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]; purity and source not reported.
Reliability	:	(3) invalid No information on dose volume administered; strain or sex tested; environmental conditions of housing; body weight changes; feed and water consumption; and control response. Low number of animals tested at dose levels below 5000 mg/kg. No characterization of test substance.

20.11.2003 (11)

Type	:	LD50
Value	:	
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	1
Vehicle	:	other: olive oil
Doses	:	500, 1000, 2000, 3000, 5000 mg/kg bw
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS
Method	:	Stannous octoate was administered in olive oil by gavage to one rabbit/dose level tested, i.e., 500, 1000, 2000, 3000, and 5000 mg/kg bw. Control animals received olive oil only. Animals were observed for 10 days, then sacrificed and examined for gross and microscopic abnormalities.
Result	:	Mortality (number of dead/total number tested), by dose level tested: 500 mg/kg: 0/1 1000 mg/kg: 0/1 2000 mg/kg: 1/1 (death occurred <16-h post-administration) 3000 mg/kg: 1/1 (death occurred <16-h post-administration)

5000 mg/kg: 1/1 (death occurred <16-h post-administration)

All animals had diarrhea and slight body weight loss. Microscopic abnormalities observed at 1000 mg/kg included slight hyperemia in the kidneys.

Source : Metal Carboxylates Coalition
Test substance : Tin (II) Ethylhexanoate [CAS No. 301-10-0]; purity and source not reported.
Reliability : (3) invalid
No information on dose volume administered; strain or sex tested; environmental conditions of housing; body weight changes; feed and water consumption; and control response. Low number of animals tested (1) at all dose levels. No characterization of test substance.

20.11.2003 (11)

Type : LD50
Value :
Species : guinea pig
Strain : no data
Sex : no data
Number of animals : 1
Vehicle : other: olive oil
Doses : 250, 500, 1000, 2000, 3000 mg/kg bw
Method : other: not reported
Year :
GLP : no
Test substance : other TS

Method : Stannous octoate was administered in olive oil by gavage to one guinea pig/dose level tested, i.e., 250, 500, 1000, 2000, and 3000 mg/kg bw. Control animals received olive oil only. Animals were observed for 10 days, then sacrificed and examined for gross and microscopic abnormalities.
Result : Mortality (number of dead/total number tested), by dose level tested:
250 mg/kg: 0/1
500 mg/kg: 1/1 (death occurred 5-d post-administration)
1000 mg/kg: 1/1 (death occurred <16-h post-administration)
2000 mg/kg: 1/1 (death occurred <16 h post-administration)
3000 mg/kg: 1/1 (death occurred <16 h post-administration)

All animals had diarrhea and slight body weight loss. Microscopic abnormalities observed at 250 mg/kg included slight hyperemia in the kidneys

Source : Metal Carboxylates Coalition
Test substance : Tin (II) Ethylhexanoate [CAS No. 301-10-0]; purity and source not reported.
Reliability : (3) invalid
No information on dose volume administered; strain or sex tested; environmental conditions of housing; body weight changes; feed and water consumption; and control response. Low number of animals tested (1) at all dose levels. No characterization of test substance.

20.11.2003 (11)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	= 535 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: olive oil
Doses	:	150, 262, 380, 452, 552, 664, 800, 1000 mg/kg bw
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method : Stannous octoate was administered by intraperitoneal injection to groups of 2 or 6 rats at dose levels ranging from 150-1000 mg/kg bw. Control animals were administered olive oil alone. Animals were observed for 10 days, surviving animals were sacrificed at the end of the observation period. All animals were examined for gross and microscopic abnormalities, either at time of death or post-sacrifice. The median lethal dose (LD50) was calculated according to the method of Weil (1952).

Result : Mortality (number of dead/total number tested), by dose level tested:
150 mg/kg: 0/6
262 mg/kg: 0/6
380 mg/kg: 0/6
452 mg/kg: 0/6
552 mg/kg: 4/6 (deaths occurred between days 6 and 8)
664 mg/kg: 6/6 (deaths occurred days 6 and 8)
800 mg/kg: 6/6 (deaths occurred days 1 and 6)
1000 mg/ kg: 6/6 (deaths occurred <16-h post-administration)

Stannous octoate given by i.p. injection caused severe peritonitis. Post mortem examination found capsulation of the liver and spleen in all animals, which extended to the stomach and intestines for animals in the high dose group. At 1000 mg/kg, the peritoneal cavity contained bloodstained fluid. Microscopic changes observed at 1000 mg/kg included minimal vacuolation of perilobular cells and liver covered with fibrous capsule.

The median lethal dose (LD50) was calculated to be 535 mg/kg bw, with 95% probability of the true value falling between 495 and 580 mg/kg bw.

Source : Metal Carboxylates Coalition

Test substance : Tin (II) Ethylhexanoate [CAS No. 301-10-0]; purity and source not reported.

Reliability : (3) invalid
No information on dose volume administered; strain or sex tested; environmental conditions of housing; body weight changes; feed and water consumption; and control response. Less than currently recommended number of animals tested per dose level. No characterization of test substance.

20.11.2003 (11)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	other: none
PDII	:	1.54
Result	:	slightly irritating
Classification	:	
Method	:	other: Draize et al. skin irritation test
Year	:	
GLP	:	no
Test substance	:	other TS

Method :

Six albino rabbits (3 males, 3 females) were used in the study. The hair was clipped on the back of each animal and two areas approximately 10-cm apart were selected as application sites. The skin at one site was abraded by making four epidermal incisions in a cross hatch pattern, the other site was left unabraded. 0.5-mL of the test material was applied to each site on each animal 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 hours, after which time the trunk bands were removed. The application sites were examined and scored at 24 and 72 hours post-treatment. Skin reactions (i.e., erythema and eschar formation and edema formation) were evaluated according to the method of Draize, Woodard, and Calvery. Skin reactions were graded 0 (no erythema or no edema), 1 (very slight erythema or edema), 2 (well-defined erythema or slight edema), 3 (moderate to severe erythema or moderate edema), or 4 (severe erythema to slight eschar formation or severe edema).

Result :

Mean (n=6) skin reaction scores for intact skin:
Erythema/Eschar Formation (24-h): 1.50
Edema Formation (24-h): 1.33

Erythema/Eschar Formation (72-h): 0.17
Edema Formation (72-h): 0

Mean (n=6) skin reaction scores for abraded skin:
Erythema/Eschar Formation (24-h): 1.33
Edema Formation (24-h): 1.50

Erythema/Eschar Formation (72-h): 0.17
Edema Formation (72-h): 0.17

The Primary Irritation Score was calculated to be 1.54, indicating the test material is mildly irritating. After 72 hours observation, almost no skin irritation was evident on any test animal.

Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]
Reliability	:	(2) valid with restrictions Very brief description of methods and results. Characterization of test material was not reported.

11.11.2003 (2)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	2
Vehicle	:	
PDII	:	
Result	:	
Classification	:	
Method	:	other: Skin irritation and acute percutaneous absorption test
Year	:	
GLP	:	no data
Test substance	:	other TS
Method	:	Test animals were two (2) female New Zealand White rabbits. Test material (2000 mg/kg) 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. Exposure duration was prolonged contact (24 h) and repeated 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.
Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]; pale yellow liquid, also known as Fomrez C-2.

13.10.2003 (9)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure time	:	
Comment	:	other: washed and unwashed
Number of animals	:	
Vehicle	:	none
Result	:	
Classification	:	
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS
Result	:	Moderate eye irritant. Undiluted test substance caused moderate conjunctivitis and swelling, accompanied by slight to moderate corneal injury in washed and unwashed eyes. Effects had not subsided after one week.
Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]
Reliability	:	(4) not assignable Documentation insufficient for assessment; provided for information only. Report lacks information on strain and sex tested, number of animals tested, number of positive findings vs. total number of animals tested,

dosing method applied, control response, and scoring method.

11.11.2003 (8)

Species	:	rabbit
Concentration	:	1 %
Dose	:	
Exposure time	:	
Comment	:	other: washed and unwashed
Number of animals	:	
Vehicle	:	other: propylene glycol
Result	:	
Classification	:	
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS
Result	:	Moderate eye irritant. The test material as a 1% solution in propylene glycol caused slight pain and conjunctivitis. Effects subsided within one week. The undiluted test material caused moderate conjunctivitis and swelling, and slight to moderate corneal injury. Effects caused by the undiluted material did not subside within one week.
Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]
Reliability	:	(4) not assignable Documentation insufficient for assessment; provided for information only. Report lacks information on strain and sex tested, number of animals tested, number of positive findings vs. total number of animals tested, dosing method applied, control response, and scoring method.

11.11.2003 (8)

5.3 SENSITIZATION

Type	:	Guinea pig maximization test
Species	:	guinea pig
Number of animals	:	
Vehicle	:	other: propylene glycol
Result	:	
Classification	:	sensitizing
Method	:	other: OECD Guide-line 406, "Skin Sensitization" (1981), Directive 84/449/EEC, B.6 (1984), and Magnusson and Klingman (1970)
Year	:	
GLP	:	yes
Test substance	:	other TS
Method	:	Female Himalayan albino guinea pigs (SPF-quality, approximately 9 weeks old) were obtained from BRL Ltd., Basel, Switzerland. Animals were acclimated to test conditions for at least 5 days prior to treatment. Animals were housed in pairs, under constant conditions of temperature (21 deg. C), relative humidity (55%), and photoperiod (12-hour light/12-hour dark). Food and water were provided ad libitum. At the end of the acclimation period, animal body weights ranged from 344-465 g. Primary irritation experiments consisting of intradermal injections (0.1 ml/site) and epidermal applications (0.1 ml) of various concentrations of the test substance were conducted to identify suitable test substance

concentrations for the main study and challenge applications, as well as identify any systemic toxic effects. Evaluations of dermal reactions from these experiments were conducted after 24 and 48 hours exposure.

MAIN STUDY
A) Induction via intradermal injections: A group of 20 animals were used for the test group; an additional 10 animals served as a control group. Immediately prior to testing, a 4 x 6 cm area in the scapular region of each animal was shaved. Three pairs of intradermal injections (0.1 mL/site) were made at the border of the shaved dorsal area on each test animal using:

(1) the test substance diluted to 2% (w/w) with propylene glycol;
(2) a 50% (v/v) Freunds' Complete Adjuvant (FCA) solution with distilled water; and
(3) a 4% (w/w) solution of the test substance emulsified in 50:50 FCA.

Control animals received the same injections as the test animals, excluding the test substance.

B) Induction via epidermal application: Seven days after the intradermal injections, the scapular area of all test and control animals was shaved. Test animals were treated with 0.5 ml of a 50% solution of the test substance in propylene glycol applied epidermally on a moistend patch secured with tape between the injection sites. Control animals were treated with propylene glycol only. After 48 hours, the dressings and residual test material were removed, and the reaction sites were immediately assessed for erythema and edema immediately.

Challenge: Test and control guinea pigs were challenged two weeks after the epidermal application. A 25 cm2 area on the left flank of each animal was shaved and a 0.05 mL application was made with each of the following:

(a) 10% (w/w) test substance in propylene glycol;
(b) 5%(w/w) test substance in propylene glycol;
(c) 2% (w/w) test substance in propylene glycol; and
(d) propylene glycol.

Challenge applications were performed using Square chambers attached to Micropore tape and held in place with elastic bandages. Dressings and residual test substance were removed after 24 hours. Sites were assessed for redness and swelling 24 and 48 hours after removal of the dressing using a numerical grading system: 0 (no skin reaction), 1 (red spots; scattered reactions), 2 (moderate but confluent redness), 3 (redness and swelling), or 4 (intense redness and swelling).

Mortality, viability, and toxicity were assessed daily. Body weights were recorded during acclimation and at termination of the study. All animals were sacrificed at study termination.

Result : During the primary irritation experiments, no signs of systemic toxicity were observed; however, body weight loss was noted in 3 of the 5 animals tested.

During the main study, no symptoms of systemic toxicity were observed and no mortality occurred. Average body weight gain of test and control animals was comparable. After the 48 hours occluded epidermal induction exposure, test animals showed slight to severe erythema and slight to well-

defined edema. In the challenge test, 20, 16 and 13 test animals showed a positive skin reaction in response to the 10%, 5% and 2% test substance concentrations, respectively.

Based on these results, a sensitization rate of 85% was determined. The test substance should be considered to have extreme sensitizing properties.

Source : Metal Carboxylates Coalition
Test substance : Tin (II) Ethylhexanoate [CAS No. 301-10-0]; Lot no. 9H114551, clear yellow liquid, also known as DABCO T-9. Purity not reported, treated as 100%. Prepared in propylene glycol.
Reliability : (1) valid without restriction
Guideline study conducted under GLP.

11.11.2003 (6)

Remark : In a contact dermal irritation/skin sensitization study with guinea pigs, following the Modified Buehler method, stannous octoate (as Fomrez C-2) caused delayed contact hypersensitivity, with 6/10 treated animals showing slight to moderate erythema.
Source : Metal Carboxylates Coalition
13.10.2003 (9)

5.4 REPEATED DOSE TOXICITY

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538
Test concentration : 0.5 - 500 µg/plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: Ames test (actual method not reported)
Year :
GLP : no data
Test substance : other TS

Method : Study was conducted at Dow Corning Corporation, Toxicology Department. Test substancewas prepared in dimethylsulfoxide (DMSO) at concentrations ranging from 0.5-500 µg/plate. The Ames Bacterial Assay was conducted both with and without metabolic activation. No details were provided regarding the metabolic activation system. An additional Spot Plate Test was conducted against each indicator organism using the undiluted test material.
Result : No evidence of genetic activity was observed.
Source : Metal Carboxylates Coalition
Test substance : Tin (II) Ethylhexanoate [CAS No. 301-10-0]
Reliability : (4) not assignable
Documentation insufficient for assessment; provided for information only. Report lacks information on metabolic activation system, characterization of test material, individual plate counts, mean number of revertent colonies per plate, and positive and negative controls used.

11.11.2003 (8)

Type	:	Cytogenetic assay
System of testing	:	L929 Mouse fibroblast cultures
Test concentration	:	8 ug - 1 mg
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS

Method : Study was conducted at St. Luke's Hospital, Bradford, Yorkshire, UK.

Test concentrations were prepared as weight % solutions of stannous octoate in acetone or chloroform, depending on the concentration range. Test solutions were spotted onto filter paper, the solvent was allowed to evaporate, and the dried papers were irradiated with a Cobalt-60 source to give a radiation dose of 2.5 mega rads.

An L929 mouse fibroblast culture was suspended in growth medium. Cell monolayers were prepared by pipetting 5-mL samples of the culture into petri dishes to produce an initial cell concentration of 1 x 10e6 cells/dish. Dishes were treated with a 5% CO2/air mixture and incubated for 24 hours at 36ºC.

The stannous octoate samples were aseptically placed in contact with the cell monolayers and incubated for 48 hours. After removal of the medium, dead cells were stained with 0.5% tryptan blue vital stain in phosphate buffered saline solution and the dishes were examined both micro- and macroscopically. Polyethylene and polyvinyl chloride were used as the nontoxic and toxic controls, respectively.

Result	:	Stannous octoate demonstrated no toxic effects to L929 mouse fibroblast cultures within the exposure range of 8 ug - 1 mg.
Source	:	Metal Carboxylates Coalition
Test substance	:	Tin (II) Ethylhexanoate [CAS No. 301-10-0]
Reliability	:	(4) not assignable Documentation insufficient for assessment. Report lacks information on individual concentrations tested, characterization of test material, replication, and results per concentration tested.

11.11.2003 (8)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

Species	:	rat
Sex	:	male/female
Strain	:	other: inbred August hooded
Route of admin.	:	oral feed
Exposure period	:	weeks 0-8, fed 1% test substance in diet; weeks 8-12, no exposure; weeks 12-80, fed 0.5% test substance in diet
Frequency of treatm.	:	feed provided daily, except Sundays

Post exposure period	:	
Doses	:	1% test substance, containing 4500 ppm Sn (weeks 0-8); 0.5% test substance, containing 2250 ppm Sn (weeks 12-80).
Result	:	
Control group	:	yes, concurrent no treatment
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method :

The test substance was dissolved in arachis oil and then mixed into powered feed (20% protein diet). Test diets were prepared twice weekly.

Treatment groups:
Group 1: 1% stannous 2-ethylhexoate (4600 ppm Sn) in 20% protein diet
Group 2: 20% protein diet only (control group)

Pregnant rats were divided into treated and control (untreated) groups. Treated pregnant rats were exposed to the 1% treated diet beginning on the day their litters were born, while pregnant control rats received untreated feed. Water was provided to all animals ad libitum. After weaning, the young were segregated by sex into groups of 8-10, then fed the same diets as their mothers. At weaning, 37 animals (17 males and 20 females) were in Group 1 and 40 animals (20 males and 20 females) in were Group 2.

After 8 weeks of exposure, the treated group was severely underweight and anemic compared to the control group. Due to this, treatment was discontinued and the animals were given control feed for 4 weeks, at which time their condition improved and body weights were comparable to the controls. At 12 weeks, exposure to the treated diet was resumed but at half the previous dose (0.5% test substance). The animals remained on this diet until death.

Animals were cursorily examined daily (except on Sunday). Body weights were measured and general examinations were conducted weekly. Sick animals were euthanized and underwent histopathological examination for tumor development and other internal changes. Survivng animals were euthanized after 80 weeks.

Result :

No mortalities were observed up to Week 8.

Week 52 - number dead/total number of animals tested, by Group:
Group 1: 6/17 males; 4/20 females
Group 2: 4/20 males; 3/20 females

Week 80 - number dead/total number of animals tested, by Group:
Group 1: 11/17 males; 6/20 females
Group 2: 8/20 males; 4/20 females

The majority of rats surviving 1 year exhibited signs of chronic respiratory disease. This continued until termination of the study at week 80. Chronic pneumonia was the primary cause of death or the reason an animal was terminated prior to the end of the study period. No other pathological changes were observed. No neoplastic lesions were observed at 1 year.

No neoplastic lesions were found at necropsy in treated animals that died during weeks 52 through 80. In the control group, lymphosarcoma of the

lung was reported. No hyperplastic or neoplastic lesions were seen in the gastrointestinal tract.

The majority of treated and untreated rats exhibited moderate or severe lung infection with wide cuffs of mononuclear cells around bronchi and vessels, and, in many cases, bronchiectatic changes. Slight degenerative changes were observed microscopically in the livers of animals from both groups. Animals receiving tin in the diet did not have an increased incidence of liver changes.

Source : Roe et al. 1965

Test substance : Tin (II) Ethylhexanoate [CAS No. 301-10-0]; source: Theodore St. Just & Co., Whitfield, Manchester, UK.

Reliability : (2) valid with restrictions
Irregular dosing schedule used. Study predates GLP. Characterization of the test substance was not reported. No analytical confirmation of test diets. No information on feed or water consumption, environmental conditions of housing, or homogeneity or stability of test diets. Single dose level of the test substance administered.

20.11.2003 (7)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : Cytotoxicity

Remark : A tissue cell culture study was conducted with stannous octoate (tin(II) ethylhexanoate, "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 these extracts were also 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.

Source : Metal Carboxylates Coalition

13.10.2003 (10)

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

(1) AME Associates. 1967. Acute Oral Toxicity Study in Rats with Stannous Octoate. Project #20-196. Conducted for M&T Chemicals, Inc., Rahway, NJ. April 18, 1967.

(2) AME Associates. 1967. Evaluation of Stannous Octoate by Draize Skin Irritation Technique. Project #20-196. Conducted for M&T Chemicals, Inc., Rahway, NJ. March 28, 1967.

(3) ATOFINA CANADA INC. Material Safety Data Sheet - FASCAT 2003 Catalyst. Printed: 5/22/02.

(4) ATOFINA CANADA INC. Material Safety Data Sheet - NIAX Stannous Octoate D-19. Printed: 9/12/03.

(5) 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.

(6) RCC NOTOX. 1992. Assesment of Contact Hypersensitivity to DABCO T-9 in the Albino Guinea Pig (Maximization Test). RCC NOTOX Project 062707. Conducted for Air Products and Chemicals Pura GmbH & Co.

(7) Roe, F.J.C., E. Boyland, and K. Millican. 1965. Effects of oral administration of two tin compounds to rats over prolonged periods. Food. Cosmet. Toxicol. 3(2):277-280.

(8) U.S. EPA/OPTS Public Files. Initial submission: data from toxicity study with stannous octoate in mice with cover letter dated 051492. TSCA Section 8ECP. Data submitted by Dow Chemical Company. Available from National Technical Information Service (NTIS) as Microfiche #OTS0539764. Produced 06/07/88; received 05/29/92.

(9) 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.

(10) 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.

(11) University of Birmingham - Department of Medical Biochemistry and Pharmacology, Food Research and Toxicology Unit. Studies on the Toxicity of Stannous Octoate, Dioctyl Tin Dilaurate and Mellite 139. December 1959.

10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

I U C L I D

Data Set

Existing Chemical	:	ID: 7772-99-8
CAS No.	:	7772-99-8
EINECS Name	:	tin dichloride
EC No.	:	231-868-0
Molecular Formula	:	Cl2Sn

Producer related part

Company	:	Parametrix Inc.
Creation date	:	02.10.2003

Substance related part

Company	:	Parametrix Inc.
Creation date	:	02.10.2003
Status	:	
Memo	:	
Printing date	:	20.11.2003
Revision date	:	
Date of last update	:	04.03.2004
Number of pages	:	72
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	
Smiles Code	:	CL[Sn]CL
Molecular formula	:	SnCl2
Molecular weight	:	189.6 g/mol
Petrol class	:	

06.10.2003

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	inorganic
Physical status	:	solid
Purity	:	> 98 % w/w
Colour	:	
Odour	:	

Attached document : Structural diagram as bitmap figure.

17.11.2003

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Stannochlor

06.10.2003

Stannous chloride

06.10.2003

Tin chloride (SnCl2)

06.10.2003

Tin protochloride

06.10.2003

Tin(II) chloride

06.10.2003

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : = 246 °C
Sublimation :
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Test substance : Tin Dichloride [CAS No. 7772-99-8]
17.11.2003 (5) (12)

Value : = 247 °C
Sublimation :
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Test substance : Tin Dichloride [CAS No. 7772-99-8]
17.11.2003 (6) (7)

2.2 BOILING POINT

Value : = 623 °C at
Decomposition :
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Test substance : Tin Dichloride [CAS No. 7772-99-8]
17.11.2003 (5) (12)

Value : = 652 °C at
Decomposition :
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Test substance : Tin Dichloride [CAS No. 7772-99-8]
17.11.2003 (6)

2.3 DENSITY

Type : relative density
Value : = 3.95 at °C
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Remark : Reported as Specific Gravity: 3.95
Test substance : Tin Dichloride [CAS No. 7772-99-8]
17.11.2003 (6)

Type : density
Value : = 3.95 g/cm³ at °C
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Remark : Reported as Density: 3.95 g/mL
Test substance : Tin Dichloride [CAS No. 7772-99-8]
17.11.2003 (5) (12)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

2.5 PARTITION COEFFICIENT

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : very soluble (> 10000 mg/L)
Stable :
Deg. product :
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Remark : Reported as "Solubility in Water: Completely soluble"
Test substance : Tin Dichloride [CAS No. 7772-99-8]
17.11.2003 (6)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	flow through
Species	:	Limanda limanda (Fish, marine)
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	> .035
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other: not reported
Year	:	
GLP	:	yes
Test substance	:	other TS

Method : A 96-h acute flow through bioassay was conducted in filtered seawater (salinity = 34.5 o/oo), with fish having a mean length and weight of 3.6 cm and 0.87 g, respectively. Fish were collected from wild populations and acclimated in the laboratory for at least 7 days. Stock solutions of the metal were prepared using distilled water. At least five metal concentrations were tested. A visible precipitate formed upon contact of the test substance with the saline medium.

The test was conducted using 20-l glass vessels. Twenty fish were exposed to each concentration tested. The pH, dissolved oxygen, temperature, and salinity were routinely monitored. Water samples were collected for analysis of total and soluble metals, using Flame-AAS. The LC50 values were determined by the probit method.

Result : Exposure conditions measured: pH, 7.7 +/- 0.8; dissolved oxygen, 7.9 +/- 0.6 mg/l; temperature, 12 +/- 1 deg. C; salinity, 34.6 +/- 0.2 o/oo.

The 24-, 48-, 72-, and 96-h LC50 values, based on measured concentrations of Sn, were reported as >0.035 mg Sn/l. Fish were reported to have exhibited labored breathing, possibly due to the turbidity present.

Source : Taylor et al. 1985

Test substance : Tin Dichloride, Dihydrate [CAS No. 10025-69-1]; analar grade, source: commercial supplier.

Reliability : (2) valid with restrictions
Comparable to a guideline study, conducted under GLP. Study lacks information on concentrations tested and control response.

18.11.2003 (26)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	64 hour(s)
Unit	:	
Analytical monitoring	:	no data
Method	:	other: Anderson (1944, 1946)
Year	:	
GLP	:	no
Test substance	:	other TS

Remark : Method References:
Anderson, B.G. 1944. Sewage Works J. 16:1156-1165.
Anderson, B.G. 1946. Sewage Works J. 18:82-87.

Daphnids (4 +/- 4 hrs old) were exposed to the test substance dissolved in Lake Erie water, for 64 hours at 25 deg. C. Upon addition of the test substance to the water, a precipitate formed and the hydrogen ion concentration increased. The apparent threshold concentration (i.e., concentration resulting in immobilization of 50% of the Daphnids) was estimated to be 0.00013 molar (24.6 ppm). The author reports that the threshold for stannous chloride was not dependent upon the hydrogen ion concentration, since toxicity was observed at a pH of 7.8; however, turbidy may have contributed to the toxicity observed.

The author reported that the concentration-immobilization time curve for this salt had not reached its "vertical assymptote at 64 hours." As such, the threshold concentration might be considerably lower than the value reported if the "trend of the curve at 64 hours continued unchanged."

Source : Anderson. 1948
Test substance : Tin Dichloride [CAS No. 7772-99-8]; source and purity not reported.
Reliability : (3) invalid
Study lacks information on replication, dilution water characteristics, group size, concentrations tested, exposure parameters, and method used to determine estimated threshold concentration. Additionally, the author reports the presence of a precipitate in the test solution.

18.11.2003 (4)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : µg/l
LC50 : = 55000
Analytical monitoring : no data
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Method : D. magna were obtained from in-house cultures. The test was initiated with organisms <= 24-h old and was conducted in duplicate test chambers containing 10 daphnids each. Daphnids were fed during the exposure period. A 16-h light photoperiod was maintained with a light intensity of ~115 ft.-c at the air-water interface.

Unfiltered Lake Superior water (strained through #20 bolting cloth) was used as the control and dilution water. The water had a pH of 7.4-8.2, total hardness of 440-530 mg/l, and an alkalinity of 410-500 mg/l. Dissolved oxygen concentrations were reported to be near saturation at all times.

The number of concentrations tested ranged from 5 to 12 (actual values not reported). The LC50 and 95% confidence limits for survival were determined by the method of Litchfield and Wilcoxon (1949).

Result : The 48-hour LC50 was reported as 55,000 ug Sn/L.
Source : Biesinger and Christensen. 1972
Test substance : Tin Dichloride [CAS No. 7772-99-8]; reagent grade, source American Chemical Society.

Reliability : (2) valid with restrictions
No response data were reported for controls or test organisms. Limited information on exposure conditions. Actual concentrations tested were not reported. Daphnids were fed during the exposure period, which may have reduced toxicity. The test substance may have sorbed onto food particles making it less bioavailable.

17.11.2003 (8)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : = 19.5 - 21.6
Analytical monitoring : no data
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Method : Wild-caught Daphnia magna were acclimated to laboratory conditions for 48 hours prior to testing. During acclimation, Daphnids were fed, but were not fed during testing. The mean and range of values of the physico-chemical properties of the test water were: pH, 7.6 (7.4-7.8); dissolved oxygen, 5.6 (5.2-6.5) ppm; total hardness, 240 (235-260) ppm as CaCO3; total alkalinity, 400 (390-415) ppm as CaCO3; calcium, 152 (145-165) ppm; magnesium, 92 (85-96) ppm; chloride, 7 (5-10) ppm; water temperature, 13 (11.5-14.5) deg. C.

Final test concentrations were based on preliminary acute static tests. All concentrations were tested twice without aeration. The test was conducted using 100 ml glass beakers. Temperature, pH, and dissolved oxygen were measured at test initiation.

Daphnids were presumed dead when no mobilization was observed and no response received from gentle prodding. Any young produced were removed and discarded. Dead animals were removed at 1, 2, 4, 8, 14, 33, and 48 hours. The LC50 and 95% confidence limits were calculated using both the Litchfield and Wilcoxon Method and the Harris Method.

Result : 24-h LC50 (95% CL):

37 (26.4-51.8) ppm Sn by Litchfield and Wilcoxon Method
38 (26.7-51.1) ppm Sn by Harris Method
Slope = 2.41 (1.69-3.45)

48-h LC50 (95% CL):

19.5 (13.5-28.3) ppm Sn by Litchfield and Wilcoxon Method
21.6 (14-30.4) ppm Snby Harris Method
Slope = 2.96 (2.11-4.14)

Source : Khangarot et al. 1987
Test substance : Tin Dichloride [CAS No. 7772-99-8]; source and purity not reported.
Reliability : (2) valid with restrictions
Study lacks information on actual concentrations tested, stability of test solutions, response by concentration tested, and age of test organisms at test initiation. No characterization of test substance.

18.11.2003 (17)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	= 21.56
Analytical monitoring	:	no data
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS

Method : D. magna were obtained from natural cultures and were fed fish food and yeast during the culture period, but not during the bioassay tests. The test was initiated with adult animals and was conducted in 200-ml beakers containing 100 mls of test water. Ten daphnids were exposed to each test substance concentration (actual values not reported) and each concentration was replicated three times. Mortality, taken as complete immobilization and lack of response to stimuli, was recorded at regular intervals. Immobilized daphnids were removed from the test solutions.

Tubewell hard water (aerated and filtered) was used as the test and dilution water. The water had a pH of 7.2-7.8, a DO concentration of 5.2-6.5 mg/l, a hardness of 235-260 mg CaCO3/l, an alkalinity of 390-415 mg CaCO3/l, a calcium concentration of 145-165 mg/l, a magnesium concentration of 85-96 mg/l, and a chloride concentration of 5-10 mg/l.

LC50 values and 95% confidence limits were calculated from mortality data using the moving average-angle method (Harris, 1959).

Result : Test temperatures ranged from 11.5 to 14.5 deg. C. Higher test concentrations of the test substance resulted in a decrease in water pH of up to 0.5 units. Control response data were not provided.

The 24-hr LC50 and 95% confidence limits for survival were reported as 38.00 (26.70-51.10) mg/l. The 48-hr LC50 and 95% confidence limits for survival were reported as 21.56 (14.00-30.40) mg/l.

Source	:	Khangarot and Ray. 1989
Test substance	:	Tin Dichloride [CAS No. 7772-99-8]; reagent grade.
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation.

17.11.2003 (16)

Type	:	static
Species	:	other aquatic crustacea: Crangonyx pseudogracilis
Exposure period	:	96 hour(s)
Unit	:	mg/l
LC50	:	= 50.1
Analytical monitoring	:	no
Method	:	other: not reported
Year	:	
GLP	:	no data
Test substance	:	other TS

Method : Amphipods (7 mm length; 1.5 mg dry weight) were exposed to eight concentrations of the test substance and an untreated control. The test was conducted in a room with a constant temperature of 13 deg. C and a 12-h light/12-h dark photoperiod. The control/dilution water had a hardness of 45-55 ppm as CaCO3, alkalinity of 40-60 ppm as CaCO3, conductivity of

300-350, and a pH of 6.7-6.8.

20-30 amphipods were exposed per concentration tested. There was no replication. The animals were not fed during the exposure period and test solutions were not aerated. The LC50 and 95% confidence limits were determined by the probit method and were based on nominal concentrations.

Result : Results of the acute static test of C. pseudogracilis:

48-h LC50 = 71.8 (68.3 - 76.8) ppm Sn
96-h LC50 = 50.1 (47.6 - 52.8) ppm Sn

Source : Martin and Holdich. 1986
Test substance : Tin Dichloride, Dihydrate [CAS No. 10025-69-1]; analar grade.
Reliability : (2) valid with restrictions
Not GLP, but scientifically sound design. Study lacks response data. Exposure concentrations not measured.

18.11.2003 (19)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Skeletonema costatum (Algae)
Endpoint : growth rate
Exposure period : 72 hour(s)
Unit : mg/l
EC50 : = .52
Limit test : no
Analytical monitoring : no
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Method : Test organisms were obtained from the University of Rhode Island, Kingston. Stock cultures were maintained in artificial seawater medium fortified with trace metals, vitamins, and nutrient salts.

Study was conducted to determine the effects of the test substance on algal population growth. 50 mL of artificial seawater growth medium was added to 150-mL capacity culture flasks and sterilized by pasteurization. The salinity and pH of the medium (after sterilization) were reported as 30 g/L and 8.1, respectively. One ml of the algal stock culture (initial cell concentration of ~2500 cells/mL) was added to the 50-mL aliquot of the sterilized growth medium. Stannous chloride was dissolved in 0.01 mL of acetone (nanograde; final conc. of acetone was 0.02%).

Five concentrations of stannous chloride, an untreated control, and an acetone control were replicated three times within each test. Nominal test concentrations were not reported. Algae were incubated for 72 hours on shakers at 60 excursions/minute, under photosynthetically-active fluorescent light. The temperature was maintained at 20 +/- 0.5 deg. C and a photoperiod of 14-h light/10-h dark. No control response data were provided. Algae cells were counted on a hemocytometer.

Result : The 72-h EC50 was estimated using the three point moving average angle method (Harris, 1959). Confidence intervals were not provided. The 72-h EC50 value for the test with S. costatum was reported as 0.325 mg/L as Sn; 0.52 mg/L as stannous chloride.

Two additional toxicity tests, using Thalassiosira pseudonana, were conducted using the same method described previously. The 72-h EC50 values for T. pseudonana were averaged and reported as 0.316 mg/L as Sn; 0.50 mg/L as stannous chloride.

In a separate study (Walsh et al. 1987), EC50 values for algal toxicity studies were calculated using three separate methods: straight-line graphical interpolation, moving average interpolation, and probit analysis.

The average of 2 independent studies using S. costatum and T. pseudonana were calculated and reported as follows:

S. costatum:
Graphical interpolation: 0.285 mg/L as Sn; 0.45 mg/L as stannous chloride
Moving average: 0.284 mg/L as Sn; 0.45 mg/L as stannous chloride
Probit: 0.286 mg/L as Sn; 0.46 mg/L as stannous chloride

T. pseudonana:
Graphical interpolation: 0.320 mg/L as Sn; 0.51 mg/L as stannous chloride
Moving average: 0.316 mg/L as Sn; 0.50 mg/L as stannous chloride
Probit: 0.321 mg/L as Sn; 0.51mg/L as stannous chloride

EC50 values calculated using each of the 3 different statistical methods were similar. Results were converted and reported as the test substance.

Source : Walsh et al. 1985, 1987
Test substance : Tin Dichloride [CAS No. 7772-99-8]; source and purity not reported.
Reliability : (2) valid with restrictions
18.11.2003 (28) (29)

Species : other algae: Synechocystis aquatilis
Endpoint : other: growth and chlorophyll-a content
Exposure period : 96 hour(s)
Unit :
Limit test : no
Analytical monitoring : no
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Method : The blue-green alga, Synechocystis aquatilis, was obtained from the Collection of Autotrophic Organisms of the Institute of Botany (Czech Republic). Algal cultures were maintained in modified liquid nutrient medium Z. Cells in the early exponential growth phase were harvested by centrifugation, washed with fresh medium (pH 7.2), and used for testing.

Stannous chloride dihydrate was tested at concentrations of 0, 1, 5, and 10 mg Sn/l. Growth was based on measurement of optical density (@ 650 nm) and chlorophyll-a content.

Tests were conducted in triplicate at a temperature of 23 deg. C and a 16-h light:8-h dark photoperiod.

Result : Stannous chloride dihydrate, at a concentration range of 1-10 mg/l, reduced growth (measured as optical density) and chlorophyll-a content of S. aquatilis. At 10 mg Sn/l, growth was reduced 54% and chlorophyll-a content was reduced 58%, relative to the control group.

Toxicity also was assessed at different pH levels: 7, 8, and 9. The largest decrease in growth and chlorophyll-a content occurred at pH 9.

The presence of humic acids reduced the toxicity of Sn.

Source : Pawlik-Skowronska et al. 1997
Test substance : Tin Dichloride, Dihydrate [CAS No. 10025-69-1]
Reliability : (2) valid with restrictions
Limited information on methods and materials. Study lacks information on test substance characterization and stability of test substance in test media. No analytical confirmation of test substance concentrations. No statistical analysis of the data.

18.11.2003 (24)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

Species : Limanda limanda (Fish, marine)
Endpoint : other: mortality
Exposure period : 21 day(s)
Unit : µg/l
LC50 : = 42000
Analytical monitoring : no data
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Method : D. magna were obtained from in-house cultures. The test was initiated with organisms <=24-h old and was conducted 250-ml glass beakers containing 200 ml of solution. Beakers were covered to minimize loss due to evaporation. A total of 20 daphnids (4 replicates of 5 daphnids) were exposed to each nominal test concentration. The number of concentrations tested ranged from 5 to 12 (actual values not reported). A 16-h light photoperiod was maintained with a light intensity of ~115 ft.-c at the air-water interface. The test temperature was maintained at 18 +/- 1 deg. C. Daphnids were transferred to fresh test medium weekly for the 3 week exposure period. The number of young produced were counted weekly, then discarded.

Unfiltered Lake Superior water (strained through #20 bolting cloth) was used as the control and dilution water. The water had a pH of 7.4-8.2, total hardness of 440-530 mg/l, and an alkalinity of 410-500 mg/l. Dissolved oxygen concentrations were reported to be near saturation at all times.

The LC50 and 95% confidence limits for survival were determined by the method of Litchfield and Wilcoxon (1949).

Result : The 21-day LC50 and 95% confidence limits for survival were reported as 42,000 (23,000-76,000) ug/l as Sn. The slope of the concentration response curve was 5.86.

The mean concentration that resulted in a 50% reproductive impairment was reported as 1,500 ug/l as Sn (slope = 4.41). The mean concentration

that resulted in a 16% reproduction impairment was reported as 350 ug/l as Sn.

At an effect concentration of 3,000 ug/l as Sn, there was a 23% decrease in body weight.

Source : Biesinger and Christensen. 1972
Test substance : Tin Dichloride [CAS No. 7772-99-8]; reagent grade, source American Chemical Society.
Reliability : (2) valid with restrictions
No response data were reported for controls or test organisms. Actual concentrations tested were not reported.

17.11.2003 (8)

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male
Number of animals	:	5
Vehicle	:	other: corn oil
Doses	:	800, 1600, 3200, and 6400 mg/kg
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method : Test animals had initial body weights ranging from 200 to 250 g and were fasted 24 hours prior to dosing. Animals were caged in groups of 5 (by dose level) and were maintained at a temperature of 72 ± 2 deg. F (22.2 ± 2 deg. C), under an 8-hour light/16-hour dark photoperiod. Food and water were provided ad libitum, except during the pre-dosing fasting period.

Two suspensions of the test material were prepared in corn oil: 10% and 25% w/v. Groups of five animals were dosed at concentrations of 800, 3200, and 6400 mg/kg, respectively using the 25% suspension; while a single group of five animals was dosed at 1600 mg/kg with the 10% suspension. The test material was administered via intragastric intubation, using a syringe and stainless steel catheter. Animals were observed for 21-days post-exposure and mortalities were recorded daily. The LD50 was calculated using the Thompson Moving Average Method.

Result : Mortality (number of dead/total number tested), by dose level tested:
800 mg/kg: 1/5
1600 mg/kg: 1/5
3200 mg/kg: 5/5
6400 mg/kg: 5/5

Animals in all dose groups were observed to be inactive following test material administration. All mortalities occurred on the day following test substance administration. The oral LD50 (+95% confidence limits) of the test substance was reported as 1744.8 (1100.9-2765.3) mg/kg.

Source	:	Metal Carboxylates Coalition
Test substance	:	Tin Dichloride [CAS No. 7772-99-8]; source: M&T Chemicals, Inc.
Reliability	:	(2) valid with restrictions Very brief description of methods and results. Characterization of test material was not reported. No pathological examinations of the test animals were conducted.

17.11.2003 (1)

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	Sprague-Dawley

Sex	:	male
Number of animals	:	5
Vehicle	:	physiol. saline
Doses	:	100, 200, 400, 800, 1600, 3200 mg/kg
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method : Test animals were obtained from Flow Laboratories. Rats had an initial average body weight of 360 g. Animals were observed for 10 days. The test substance was prepared as a suspension in 0.85% saline and administered by oral intubation. Animals were observed for 10 days after exposure.

The LD50 and confidence limits were determined by the method of Litchfield and Wilcoxon.

Result : Mortality (number of dead/total number tested), by dose level tested:
100 mg/kg: 0/5
200 mg/kg: 0/5
400 mg/kg: 0/5
800 mg/kg: 3/5
1600 mg/kg: 5/5
3200 mg/kg: 5/5

All deaths occurred on days 1 and 2 following test substance administration. Animals in the 800, 1600, and 3200 mg/kg dose groups had ulceration of the stomach and red intestinal lining.

The LD50 (+95% confidence limits) of the test substance was reported as 720 (371-1398) mg/kg. The slope of the dose-response curve was 1.941.

Source : Metal Carboxylates Coalition

Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.

Reliability : (2) valid with restrictions
Study predates GLP. Very brief description of methods and results. Characterization of test material was not reported.

20.11.2003 (18)

Type	:	LD50
Value	:	
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male
Number of animals	:	6
Vehicle	:	no data
Doses	:	1500, 1700, 1930, 2200, and 2500 mg/kg
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method : Test animals were obtained from Flow Laboratories. Rats had an initial average body weight of 455 g. Animals were observed for 7 days. The test substance was prepared as a 17-28% (w/v) suspension and administered as a single dose by oral intubation. Surviving animals were sacrificed and necropsied.

The LD50 and confidence limits were determined by the method of Litchfield and Wilcoxon.

Result : Mortality (number of dead/total number tested), by dose level tested:
1500 mg/kg: 1/6 (animal died Day 1)
1700 mg/kg: 4/6 (1 animal each died Days 1 and 6; 2 animals died Day 3)
1930 mg/kg: 3/6 (animals died Day 3)
2200 mg/kg: 6/6 (2 animals each died Days 3 and 4; 1 animal each died Days 5 and 6)
2500 mg/kg: 6/6 (1 animal each died Days 2, 4, 5, and 6; 2 animals died Day 3)

No gross pathology findings at all dose levels. Signs of toxicity observed included depressed activity, excessive secretory activity resulting in crusting around the nose and eyes, and poor hair coat appearance. No gross findings were observed at necropsy.

The LD50 (+95% confidence limits) of the test substance was reported as 1723 (1469-1905) mg/kg.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.
Reliability : (2) valid with restrictions
Study predates GLP. Very brief description of methods and results. Characterization of test material was not reported.

20.11.2003 (18)

Type : other
Value :
Species : rat
Strain : Fischer 344
Sex : male/female
Number of animals : 10
Vehicle : water
Doses : 93.75, 187.5, 375, 750, and 1500 mg/kg bw
Method : other: NTP protocol
Year :
GLP : no data
Test substance : other TS

Method : Male and female F344/N rats (~6 weeks old) were obtained from Frederick Cancer Research Center, Frederick, MD, USA, and acclimated to laboratory conditions for 10 days prior to test initiation. Animals were caged in groups of 5 and food and water were provided ad libitum.

Stannous chloride, prepared in acidified distilled water (pH 1 w/ HCl), was administered in a single-dose study via gavage, to groups of 5 male and 5 female F344/N rats at doses of 93.75, 187.5, 375, 750, or 1500 mg/kg bw. Animals were observed twice daily for mortality; surviving animals were sacrificed on day 16. No necropsies were performed.

Result : Mortality (number of surviving animals/total number tested), by dose administered:
93.75 mg/kg bw: 5/5 males, 5/5 females
187.5 mg/kg bw: 5/5 males, 5/5 females
375 mg/kg bw: 5/5 males, 5/5 females
750 mg/kg bw: 5/5 males, 4/5 females (death on day 3)
1500 mg/kg bw: 5/5 males, 4/5 females (death caused by gavage

accident)

Source	:	NTP. 1982
Test substance	:	Tin Dichloride [CAS No. 7772-99-8]; anhydrous, food grade ~98.5% purity, source: M&T Chemicals, Inc.
Reliability	:	(2) valid with restrictions Pre-chronic, single-dose study. No control group included.

20.11.2003 (23)

Type	:	other
Value	:	
Species	:	mouse
Strain	:	B6C3F1
Sex	:	male/female
Number of animals	:	10
Vehicle	:	water
Doses	:	150, 300, 600, 1200, or 2400 mg/kg bw
Method	:	other: NTP protocol
Year	:	
GLP	:	no data
Test substance	:	other TS

Method	:	Male and female B6C3F1/N mice (~6 weeks old) were obtained from Frederick Cancer Research Center, Frederick, MD, USA, and acclimated to laboratory conditions for 10 days prior to test initiation. Animals were caged in groups of 5 and food and water were provided ad libitum. Stannous chloride, prepared in acidified distilled water (pH 1 w/ HCl), was administered in a single-dose study via gavage to groups of 5 male and 5 female B6C3F1/N mice at doses of 150, 300, 600, 1200, or 2400 mg/kg. Animals were observed twice daily for mortality; surviving animals were sacrificed on day 16. No necropsies were performed.
Result	:	Mortality (number of surviving animals/total number tested), by dose administered: 150 mg/kg: 5/5 males, 5/5 females 300 mg/kg: 5/5 males, 5/5 females 600 mg/kg: 4/5 males, 4/5 females (deaths occurred on day 3) 1200 mg/kg: 4/5 males, 5/5 females (death occurred on day 3) 2400 mg/kg: 0/5 males, 0/5 females (Male deaths occurred on days 2 (4 animals) and 3 (1 animal); all female deaths occurred on day 2)
Source	:	NTP. 1982
Test substance	:	Tin Dichloride [CAS No. 7772-99-8]; anhydrous, food grade ~98.5% purity, source: M&T Chemicals, Inc.
Reliability	:	(2) valid with restrictions Pre-chronic, single-dose study. No control group included.

20.11.2003 (23)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	.5 g
Exposure	:	Semiocclusive
Exposure time	:	
Number of animals	:	3
Vehicle	:	water
PDII	:	
Result	:	corrosive
Classification	:	
Method	:	other: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion" (1992), Directive 92/69/EEC, B.4 (1992), and the United Nations "Recommendations on the Transport of Dangerous Goods".
Year	:	1992
GLP	:	yes
Test substance	:	other TS

Method :

Three New Zealand White rabbits, 12-16 weeks old and ranging in body weight from 2.58 to 3.10 kg, were used for testing. Animals were obtained from David Percival Ltd. (UK), and acclimated to laboratory conditions for a minimum of 5 days prior to testing. Food and water were provided ad libitum. Animals were individually housed under controlled conditions of temperature (17-23 deg. C), humidity (30-70%), and light (12-h light/dark photoperiod).

The backs of the animals were shaved one day prior to testing. The test substance (0.5 g moistened in 0.3 ml distilled water) was applied to separate areas on the backs of each animal for 3-minute and 1-hour exposures under semi-occlusive dressings. A single animal was also treated similarly for a 4-hour exposure.

Dressings were removed at the end of each respective treatment period and residual test material was removed with cotton wool soaked in distilled water. Treatment sites were observed for irritative and corrosive effects at approximately 1, 24, 48, and 72 hours post-removal. Additional observations were conducted at days 7 and 14, in order to determine the reversibility of any observed reactions. Reactions were scored according to Draize (1977). Scoring for evaluation of skin reactions:
0 = no erythema; no edema
1 = very slight erythema; very slight edema
2 = well-defined erythema; slight edema
3 = moderate to severe erythema; moderate edema
4 = severe erythema; severe edema

Result :

4-hour exposure:
Potential white dermal necrosis; slight edema and loss of skin elasticity and flexibility; well-defined erythema surrounding skin reactions at the 24, 48, and 72-hour observation periods; sunken, hardened brown/black scab at treated skin sites at 7-day observation period.

1-hour exposure:
Well-defined erythema and slight edema; possible small necrotic foci; loss of skin elasticity and flexibility. Small scattered scabs were present around the treatment area at the 7-day observation period. At the 14-day observation period, no scabs were present (meaning the test material was not corrosive after 1-hour exposure) and the skin sites on the two

remaining animals appeared normal.

3-minute exposure:
Well-defined erythema and very slight edema. At the 7-day observation period, crust formation and slight desquamation were observed. At the 14-day observation period, the skin sites on the two remaining animals appeared normal.

Tin dichloride was determined to be corrosive to rabbit skin.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; anhydrous, white crystalline solid, source: William Blythe Ltd.
Reliability : (1) valid without restriction
Guideline study conducted under GLP.

17.11.2003 (11)

Species : rabbit
Concentration : no data
Exposure : no data
Exposure time : 72 hour(s)
Number of animals : 6
Vehicle : no data
PDII : .66
Result : slightly irritating
Classification :
Method : other: Department of Transportation, Code 49, Section 173:343.
Year :
GLP : no
Test substance : other TS

Method : The test substance was applied to both intact and abraded skin of 6 rabbits. Application sites were observed after 4, 24, and 72 hours of exposure for signs of erythema/eschar or edema formation. Skin reactions were graded and used to calculate a primary skin irritation index score.
Result : The Primary Skin Irritation index was calculated to be 0.66, indicating that the test material was a mild irritant.
Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; anhydrous, white flakes.
Reliability : (4) not assignable
Documentation insufficient for assessment. Provided for information only.

17.11.2003 (30)

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals : 6
Vehicle : other: none
PDII : 1.38
Result : slightly irritating
Classification :
Method : Draize Test
Year :
GLP : no
Test substance : other TS

Method : Six albino rabbits (3 males, 3 females) were used in the study. The hair

was clipped on the back of each animal and two areas approximately 10-cm apart were selected as application sites. The skin at one site was abraded by making four epidermal incisions in a crosshatch pattern; the other site was left unabraded. 0.5 g of test material was applied to each site on each animal and covered with gauze. The trunk was wrapped in polyethylene sheeting and taped.

The test material was left in contact with the skin for 24 hours, at which time the application sites were uncovered. Sites were examined and scored at 24 and 72 hours post-treatment. Skin reactions (i.e., erythema and eschar formation and edema formation) were evaluated according to the method of Draize, Woodard, and Calvery. Skin reactions were graded 0 (no erythema; no edema), 1 (very slight erythema; very slight edema), 2 (well-defined erythema; slight edema), 3 (moderate to severe erythema; moderate edema), or 4 (severe erythema to slight eschar formation; severe edema).

Result : Mean (n=6) skin reaction scores for intact skin:
Erythema/Eschar Formation (24-h): 1.17
Edema Formation (24-h): 1.17

Erythema/Eschar Formation (72-h): 0
Edema Formation (72-h): 0.17

Mean (n=6) skin reaction scores for abraded skin:
Erythema/Eschar Formation (24-h): 1.50
Edema Formation (24-h): 1.33

Erythema/Eschar Formation (72-h): 0.17
Edema Formation (72-h): 0

The Primary Irritation Score was calculated to be 1.38, indicating the test material is mildly irritating. After 72 hours observation, almost no skin irritation was evident on any test animal.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; source: M&T Chemicals, Inc.
Reliability : (2) valid with restrictions
Very brief description of methods and results. Characterization of test material was not reported. Test material concentration not reported.

17.11.2003 (3)

Species :
Concentration : 100 %
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result :
Classification : highly corrosive (causes severe burns)
Method : other: Corrositex Test Method to Evaluate Dermal Corrosivity.
Year :
GLP : no data
Test substance : other TS

Method : The Corrositex test procedure involves 3 steps: qualification, categorization, and classification.

1. Qualify: 100 mg of the test substance was added to the appropriate test vessel. The test vessel was shaken to dissolve the solids and allowed to stand for 1 minute. Vessel contents were observed for any noticeable color change. If color change was evident, the test proceeded to step 2.

2. Categorize: 100 mg of the test substance was added to the appropriate test vessel (Tube "A" or "B", depending on the pH of a 10% aq. solution of the substance). Vessels were shaken until mixed. Vessels were observed for noticeable color change. If no color change was noted, 2 drops of a "Confirm" reagent was added to Tube "B" and the solution was re-shaken and observed for color change. Color observed was matched with the test guide, the substance was assigned to the appropriate category, and the test proceeded to step 3.

3. Classify: 500 mg of the test substance was added to each of 4 replicate test vials containing a synthetic biobarrier. Positive (NaOH) and negative (not specified) controls are tested concurrently. Test substance that permeates the biobarrier induces a color chance in the reagent below. The time required for an evident color change is measured and used to assign a UN Packing Group classification for the test substance.

Remark : The Corrositex test is a standardized test used to predict the in vivo corrosive potential of a test material by measuring the amount of time required for the material to pass through or destroy a synthetic biobarrier. Based on the results of this test, the material may be assigned a Packing Group classification according to the hazardous material transport regulations of the USDOT and other international regulatory agencies.

Result : 1. A positive result (color change) was noted for the test substance.

2. The pH of a 10% aq. solution of the test substance was 1.4. Substance was tested in Tube A. Reaction produced a purple color in Tube A, and the solution pH was 2.2. The substance was assigned to Category 1.

3.
Time required for biobarrier permeation, by test replicate:
Replicate 1: 1.25 min.
Replicate 2: 1.5 min.
Replicate 3: 1.5 min.
Replicate 4: 1.25 min.

Mean time = 1.375 minutes

Based on the Category 1 designation of the test substance, the UN Packing Group classification was assigned based on the following time intervals:
PG I: 0 - 3 minutes
PG II: >3 - 60 minutes
PG III: >60 - 240 minutes
Non-Corrosive: >240 minutes

Based on the length of time required for the test substance to degrade and permeate the synthetic biobarrier (1.4 minutes), the test substance was classified as a Packing Group I material (Severe Corrosivity).

Source : Metal Carboxylates Coalition

Test substance : Tin Dichloride [CAS No. 7772-99-8]; anhydrous, white solid flakes, 99.4% purity, source: ATOFINA Chemicals, Inc.

Reliability : (2) valid with restrictions
Non-guideline method.

17.11.2003 (10)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 other: g
Exposure time	:	72 hour(s)
Comment	:	not rinsed
Number of animals	:	6
Vehicle	:	none
Result	:	highly irritating
Classification	:	
Method	:	Draize Test
Year	:	
GLP	:	no
Test substance	:	other TS

Method : Six albino rabbits (3 males, 3 females) were used in the study. Single 0.1 g doses of the test substance were placed directly into the conjunctival sac of the left eye of each test animal. The untreated right eye of each animal served as a control. Examinations for evidence of eye irritation were conducted at 24, 48, and 72 hours post-instillation.

Evaluations of ocular irritation (corneal opacity, corneal damage, iris reaction, and conjunctivae redness, chemosis, and discharge) were scored according to the Draize scale for scoring ocular lesions. The maximum total possible score (110 points) was the sum of all corneal, iris, and conjunctivae scores at each observation.

Result : The mean (n=6) eye irritation scores at the 24, 48, and 72-hour observations were 110, 110, and 108.6, respectively. The test substance was determined to be severely irritating to the eye of albino rabbits, based on the Draize scoring method.

Source : Metal Carboxylates Coalition

Test substance : Tin Dichloride [CAS No. 7772-99-8]; source: M&T Chemicals, Inc.

Reliability : (2) valid with restrictions
Very brief description of methods and results. Characterization of test material was not reported.

17.11.2003 (2)

5.3 SENSITIZATION

Type	:	Patch-Test
Species	:	human
Number of animals	:	
Vehicle	:	other: 1%, 5%, and 10% pet.
Result	:	
Classification	:	
Method	:	other: Patch-test
Year	:	
GLP	:	no data
Test substance	:	other TS

Method : 2,206 patients were patch tested with stannous chloride dihydrate in 1%

pet., using Finn Chambers on Scanpor tape. In a small number of patients, patch tests with stannous chloride dihydrate in 5% pet. (25 patients) and 10% pet. (19 patients) were performed. In most patients, patch tests were read on days 2, 3, and 7. Punch biopsies were performed from positive test reactions.

Result : Stannous chloride dihydrate in 1% pet.:
5 patients (4 females, 1 male) had positive (+ or ++) reactions. Punch biopsies were performed in 3 females and 1 male. All biopsies showed slight edema and spongiosis; 1 biopsy showed single cell necrosis. All reactions were determined to be allergic. The number of inconclusive and irritant reactions observed were 15 and 10, respectively.

Stannous chloride dihydrate in 5% pet.:
Of 25 patients tested, 1 had a positive reaction and 5 had an irritant reaction.

Stannous chloride dihydrate in 10% pet.:
Of 19 patients tested, 11 had an irritant reaction and 8 had a negative reaction.

The authors reported that stannous chloride dihydrate in 1% pet. is not likely to be a skin irritant. The positive patch test reactions to stannous chloride dihydrate in 1% pet. are more likely true allergic reactions.

Source : de Fine Olivarius et al. 1993

Test substance : Tin Dichloride, Dihydrate [CAS No. 10025-69-1]; >99.9% purity, source: Merck.

Reliability : (2) valid with restrictions

18.11.2003 (9)

5.4 REPEATED DOSE TOXICITY

Type : Sub-acute
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 14 days
Frequency of treatm. : daily, continuous in diet
Post exposure period :
Doses : 1900, 3800, 7500, 15000, and 30000 ppm
Control group : no
Method : other: NTP protocol
Year :
GLP : no data
Test substance : other TS

Method : Male and female F344/N rats (~6 weeks old) were obtained from Frederick Cancer Research Center, Frederick, MD, USA, and acclimated to laboratory conditions for 10 days prior to test initiation. Animals were caged in groups of 5 and food and water were provided ad libitum.

Stannous chloride was administered in oral feed to groups of 5 male and 5 female F344/N rats. Test diets contained 1900, 3800, 7500, 15,000, or 30,000 ppm stannous chloride. No control group was included. Animals were observed twice daily for mortality. Necropsies were performed on all animals at the end of the 14-day study period.

Result	:	There were no mortalities during the 14-day study period. Animals fed 30,000 ppm stannous chloride in the diet had roughened coats and distended abdomens. All 5 female rats and 3 of 5 male rats receiving 30,000 ppm stannous chloride in the diet lost weight. Weight gains decreased with increasing dose levels.
Source	:	NTP. 1982
Test substance	:	Tin Dichloride [CAS No. 7772-99-8]; anhydrous, food grade ~98.5% purity, source: M&T Chemicals, Inc.
Reliability	:	(2) valid with restrictions Pre-chronic study. No control group included.

20.11.2003 (23)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	13 weeks
Frequency of treatm.	:	daily, continuous in diet
Post exposure period	:	
Doses	:	500, 1000, 1900, 3800, or 7500 ppm
Control group	:	yes, concurrent no treatment
Method	:	other: NTP protocol
Year	:	
GLP	:	no data
Test substance	:	other TS

Method :

Male and female F344/N rats (4 week old) were obtained from Frederick Cancer Research Center, Frederick, MD, USA, and acclimated to laboratory conditions for 10 days prior to test initiation. Animals were caged in groups of 5, and dosed feed, control feed, and water were provided ad libitum.

Stannous chloride was administered in oral feed to groups of 10 male and 10 female F344/N rats. Test diets contained 0, 500, 1000, 1900, 3800, or 7500 ppm stannous chloride. Animals were observed twice daily for mortality and signs of toxicity. Animals were given clinical examinations weekly. Body weight and food consumption were recorded weekly. Necropsies were performed on all animals at time of death or at the end of the 13-week study period.

Examinations performed in the control and high dose groups included: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, and pituitary.

Result :

There were no mortalities during the 13-week study period. Mean body weight gain was reduced more than 12% in animals receiving the 7500 ppm diet, relative to control animals. However, average daily feed consumption at 7500 ppm was higher than that of the control group.

70-100% of rats receiving the 3800 or 7500 ppm diets had gross distention of the cecum and reddened gastric mucosa, although no compound-related histopathologic effects were observed in the cecum, stomach, or any other tissues examined.

Based on the results of the 13-week study, doses of 1000 and 2000 ppm stannous chloride in feed were selected for the chronic, 105-week study.

Source : NTP. 1982
Test substance : Tin Dichloride [CAS No. 7772-99-8]; anhydrous, food grade ~98.5% purity, source: M&T Chemicals, Inc.
Reliability : (2) valid with restrictions
Pre-chronic study.

20.11.2003 (23)

Type : Sub-acute
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 14 days
Frequency of treatm. : daily, continuous in diet
Post exposure period :
Doses : 1900, 3800, 7500, 15000, and 30000 ppm
Control group : no
Method : other: NTP program
Year :
GLP : no data
Test substance : other TS

Method : Male and female B6C3F1/N mice (~6 weeks old) were obtained from Frederick Cancer Research Center, Frederick, MD, USA, and acclimated to laboratory conditions for 10 days prior to test initiation. Animals were caged in groups of 5 and food and water were provided ad libitum.

Stannous chloride was administered in oral feed to groups of 5 male and 5 female B6C3F1/N mice. Test diets contained 1900, 3800, 7500, 15,000, or 30,000 ppm stannous chlorides. No control group was included. Animals were observed twice daily for mortality. Necropsies were performed on all animals at the end of the 14-day study period.

Result : There were no mortalities during the 14-day study period. All animals gained weight; however, female mice fed diets of 15,000 or 30,000 ppm stannous chloride gained less weight than animals in the lower treatment groups.
Source : NTP. 1982
Test substance : Tin Dichloride [CAS No. 7772-99-8]; anhydrous, food grade ~98.5% purity, source: M&T Chemicals, Inc.
Reliability : (2) valid with restrictions
Pre-chronic study. No control group included.

20.11.2003 (23)

Type : Sub-chronic
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 13 weeks
Frequency of treatm. : daily, continuous in diet
Post exposure period :
Doses : 1900, 3800, 7500, 15,000 and 30,000 ppm
Control group : yes, concurrent no treatment
Method : other: NTP protocol

Year	:	
GLP	:	no data
Test substance	:	other TS
Method	:	Male and female B6C3F1/N mice (5 week old) were obtained from Frederick Cancer Research Center, Frederick, MD, USA, and acclimated to laboratory conditions for 10 days prior to test initiation. Animals were caged in groups of 5, and dosed feed, control feed, and water were provided ad libitum. Stannous chloride was administered in oral feed to groups of 10 male and 10 female B6C3F1/N mice. Test diets contained 0, 1900, 3800, 7500, 15,000 and 30,000 ppm stannous chloride. Animals were observed twice daily for mortality and signs of toxicity. Animals were given clinical examinations weekly. Body weight and food consumption were recorded weekly. Necropsies were performed on all animals at time of death or at the end of the 13-week study period. Examinations performed in the control and high dose groups included: gross lesions, tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, bone marrow, thymus, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder, pancreas, spleen, kidneys, adrenals, bladder, seminal vesicles/prostate/testes or ovaries/uterus, brain, and pituitary.
Result	:	There were no mortalities during the 13-week study period. Mean body weight gain was reduced more than 30% in female mice and more than 55% in male mice receiving the 30,000 ppm diet, relative to control animals. However, average daily feed consumption in male mice at 30,000 ppm was higher than that of the control group. 60-90% of male mice and 30-100% of female mice receiving diets of >=3800 ppm had gross distention of the cecum. No compound-related histopathologic effects were observed in the cecum, stomach, or any other tissues examined. Based on the results of the 13-week study, doses of 1000 and 2000 ppm stannous chloride in feed were selected for the chronic, 105-week study.
Source	:	NTP. 1982
Test substance	:	Tin Dichloride [CAS No. 7772-99-8]; anhydrous, food grade ~98.5% purity, source: M&T Chemicals, Inc.
Reliability	:	(2) valid with restrictions Pre-chronic study.

20.11.2003 (23)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Bacterial reverse mutation assay
System of testing	:	Salmonella typhimurium TA1535, TA1537, TA97, TA98, TA100
Test concentration	:	0, 3.3, 10, 33, 100, 333 µg/plate
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Salmonella/mammalian microsome assay, preincubation modification (Haworth et al.)
Year	:	1983

GLP : no data
Test substance : other TS

Method : Bacterial strains TA1535, TA1537, TA97, TA98, and TA100 were obtained from Dr. Bruce Ames, University of California, Berkeley, USA. Testing was conducted at Case Western Reserve University.

Metabolic Activation: The S9 homogenate was prepared from the livers of Aroclor 1254-induced male Sprague Dawley rats and male Syrian hamsters. The S9 mix, prepared immediately prior to testing, consisted of 0.10 ml S9 fraction, 0.02 ml 0.04 M MgCl2, 0.02 ml 1.65 M KCl, 0.10 0.04 M NADP, 0.10 ml 0.05 M glucose-6-phosphate, 0.10 ml 1.0 M NaH2PO4 (pH 7.4), and 0.56 ml distilled water.

Test substance concentrations tested in triplicate: 0, 3.3, 10, 33, 100, and 333 ug/plate. Concentrations of the test substance were prepared in distilled water (solvent control). Positive controls tested concurrently included sodium azide (for TA1535 and TA100), 4-nitro-o-phenylenediamine (for TA98), and 9-aminoacredine (for TA97 and TA1537). 2-Aminoanthracene was used in tests with metabolic activation.

Each 13 x 100-mm test tube used contained 0.5 ml S9 mix or 0.1 M PO4 buffer, 0.05 ml of culture, and 0.5 ml of solvent or test substance dilution. Tubes were mixed and incubated without shaking at 37 deg. C for 20 minutes, then 2.0 ml of molten top agar supplemented with 0.5 mM L-histidine and 0.5 mM D-biotin were added. Tubes were mixed and poured onto 25 ml of minimal glucose bottom agar in petri dishes. Solidified dishes were inverted and incubated at 37 deg. C for 48 hours.

The criteria for data evaluation were as follows:
Mutagenic Response: a dose-related, reproducible increase in the number of revertants over background, even if the increase was less than twofold.
Non-mutagenic Response: no increase in the number of revertants.
Questionable Response: absence of a clear dose-release increase in revertants, dose-related increase in numbers of revertants is not reproducible, or response was not large enough to support a determination of mutagenicity.

Result : Results (mean [SEM]) of the bacterial reverse mutation assay of stannous chloride, by bacterial strain tested and dose:

TA100 w/o metabolic activation:
Solvent control: 126 (6.6)
3.3 ug/plate: 126 (5.5)
10 ug/plate: 130 (6.7)
33 ug/plate: 130 (1.7)
100 ug/plate: 127 (0.5)
333 ug/plate: 130 (1.2)
Positive control: 855 (32.2)

TA100 with hamster liver S9/rat liver S9:
Solvent control: 149 (7.5)/ 157 (7.3)
3.3 ug/plate: 146 (2.2)/ 145 (4.3)
10 ug/plate: 144 (5.5)/ 147 (5.7)
33 ug/plate: 137 (7.5)/ 131 (1.2)
100 ug/plate: 136 (9.4)/ 138 (1.9)
333 ug/plate: 134 (3.4)/ 133 (0.0)
Positive control: 1666 (78.4)/2045 (155.0)

TA1535 w/o metabolic activation:
Solvent control: 18 (3.5)
3.3 ug/plate: 16 (2.7)
10 ug/plate: 16 (3.5)
33 ug/plate: 21 (1.0)
100 ug/plate: 18 (0.9)
333 ug/plate: 11 (2.7)
Positive control: 883 (15.7)

TA1535 with hamster liver S9/rat liver S9:
Solvent control: 26 (0.9)/ 23 (2.5)
3.3 ug/plate: 29 (1.5)/ 28 (1.5)
10 ug/plate: 25 (2.4)/ 25 (1.0)
33 ug/plate: 26 (2.4)/ 24 (1.2)
100 ug/plate: 25 (1.0)/ 26 (1.2)
333 ug/plate: 21 (1.0)/ 23 (2.5)
Positive control: 299 (31.2)/356 (25.6)

TA1537 w/o metabolic activation:
Solvent control: 8 (0.9)
3.3 ug/plate: 9 (0.9)
10 ug/plate: 8 (0.9)
33 ug/plate: 11 (2.6)
100 ug/plate: 11 (2.6)
333 ug/plate: 10 (1.7)
Positive control: 152 (20.9)

TA1537 with hamster liver S9/rat liver S9:
Solvent control: 21 (1.5)/ 19 (0.5)
3.3 ug/plate: 22 (1.2)/ 17 (1.2)
10 ug/plate: 26 (1.0)/ 16 (1.9)
33 ug/plate: 24 (1.5)/ 17 (1.2)
100 ug/plate: 25 (0.9)/ 19 (0.0)
333 ug/plate: 24 (1.5)/ 15 (2.0)
Positive control: 104 (5.8)/183 (10.3)

TA98 w/o metabolic activation:
Solvent control: 28 (2.0)
3.3 ug/plate: 25 (1.7)
10 ug/plate: 30 (1.8)
33 ug/plate: 24 (5.5)
100 ug/plate: 24 (0.3)
333 ug/plate: 28 (1.2)
Positive control: 252 (19.5)

TA98 with hamster liver S9/rat liver S9:
Solvent control: 37 (1.2)/ 37 (0.9)
3.3 ug/plate: 32 (1.8)/ 30 (2.4)
10 ug/plate: 33 (2.9)/ 30 (1.3)
33 ug/plate: 33 (2.6)/ 24 (5.0)
100 ug/plate: 31 (0.9)/ 34 (1.0)
333 ug/plate: 32 (2.1)/ 26 (0.6)
Positive control: 964 (180.6)/1394 (147.6)

It is concluded that stannous chloride was not mutagenic under the conditions employed in this study.

Source	:	Mortelmans et al. 1986
Test substance	:	Tin Dichloride [CAS No. 7772-99-8]; >99% purity, source: M&T Chemicals.
Reliability	:	(2) valid with restrictions Guideline study without detailed documentation.

19.11.2003 (21)

Type	:	other: Chromosomal aberration test and Sister chromatid exchange assay
System of testing	:	Chinese hamster ovary (CHO) cells
Test concentration	:	0-1500 ug/ml
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	positive
Method	:	other: Galloway et al. (with modifications)
Year	:	1985
GLP	:	no data
Test substance	:	other TS

Method :

Stannous chloride was tested for induction of chromosomal aberrations (ABS) and sister chromatid exchanges (SCE) in Chinese hamster ovary (CHO) cells.

Mycoplasma-free CHO cells were obtained from Litton Bionetics. Cells were maintained in McCoy's 5A medium supplemented with L-glutamine (2 mM), antibiotics, and 10% fetal bovine serum (FBS). Cultures were maintained at 37 deg. C, a relative humidity of 95%, and a 5% CO2 in air atmosphere.

Dimethyl sulfoxide (DMSO) was used as the solvent. Concurrent positive and solvent controls were included in all tests. The positive controls were MMC or CP. A number of independent assays were conducted at various concentration levels.

Metabolic Activation: The S9 homogenate was prepared from the livers of Aroclor 1254-induced male Sprague Dawley rats. The final concentrations of S9, NADP, and isocitric acid were 0.02 ml, 2.4 mg, and 4.5 mg, respectively, per ml of culture medium.

SCE assay:
1 x 10e6 cells were seeded per 75 cm2 flask. For assays without metabolic activation, cells were treated with test or control substances for 2 hours before bromodeoxyridine (BrdU) was added (10 uM final concentration). Cells were incubated for an additional 24 hours. Thereafter, the medium was removed, fresh medium containing 10 uM BrdU and colcemid was added, and incubation continued for an additional 2-3 hours. For assays with metabolic activation, cells were rinsed twice with phosphate buffered saline (PBS). Culture medium without FBS was added. Cells were incubated for 2 hours in the presence of the test or control substances and the S9 mixture. After 2 hours, cells were washed twice with PBS, then complete medium containing 10% FBS and 10 uM BrdU was added. Cells were incubated an additional 26 h with colcemid present during the last 2-3 h of incubation. 2-3 h after the addition of colcemid, cells were harvested, treated with hypotonic KCl (75 mM), washed with a fixative (3:1 methanol:glacial acetic acid, v/v), placed on slides, and air dried. Cells were stained for the detection of SCE with Giemsa. 50 second division metaphase cells were scored per dose for the incidence of SCE. The number of chromosomes in each cell was recorded.

ABS assay:
1.2 x 10e6 cells were seeded per 75 cm2 flask. For assays without metabolic activation, the method used was similiar to the SCE assay except that cells were treated for approx. 10 hours and BrdU was not used. 2-3 hours prior to cell harvest, colcemid was added. For assays with metabolic activation, the method used was also similar to the SCE assay except that BrdU was omitted and cells were harvested approx. 11 hours after removal of the S9 fraction. 2 h prior to harvest, colcemid was added. Slides were stained in 6% Giemsa for 5-10 min. 200 cells were scored for each dose level. Only metaphase cells in which the chromosome number was between 19 and 23 were scored. The chromosome number was recorded for each cell and chromosome or chromatid type aberrations were classified as follows: simple (breaks, fragments, double minutes), complex (interchanges, rearrangements), and other (pulverized, more than 10 aberrations/cell).

Result : Stannous chloride exposed CHO cells, both in the presence and absence of the S9 metabolic activation system, increased sister chromatid exchanges and chromosome aberrations. A dose-related increase in SCE induction was observed only following delayed harvest (26-36 h). The effect was observed both with and without S9. A precipitate was visible at 500 ug/ml.
Source : Gulati et al. 1989
Test substance : Tin Dichloride [CAS No. 7772-99-8]; >99% purity; source: M&T Chemicals.
Reliability : (2) valid with restrictions
Comparable to guideline study with acceptable restrictions. Raw data for a number of independent assays are provided.

19.11.2003 (15)

Type : Mammalian cell gene mutation assay
System of testing : L5178Y mouse lymphoma cells
Test concentration : 0-80 ug/ml
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other: Clive et al. (1979), Mitchell et al. (1988), and Myhr and Caspary (1988)
Year :
GLP : no data
Test substance : other TS

Method : L5178Y mouse lymphoma cells, mycoplasma free, were obtained from Dr. D. Clive, Burroughs Wellcome Co., Research Triangle Park, NC. Cultures (1 x 10e6 cells/ml) were maintained in growth medium containing 9% DMSO. Cultures used for the assays were maintained in RPM1 1640 or Fischer's medium. For mutation assays, subcultures were established in medium containing THMG [3 ug/ml thymidine, 5 ug/ml hyposanthine, 0.1 ug/ml methotrexate, and 7.5 ug/ml glycine added to Fisher's growth medium (or 3x these amounts added to RPM1 1640 medium)]. After growth for 24 hours, cells were transferred to THG medium (without methotrexate).

Metabolic Activation: The S9 homogenate was prepared from the livers of Aroclor 1254-induced male Fischer 344 rats. The vehicle was 0.15M KCl. S9 was mixed prior to use with phosphate-buffered saline (PBS), a neutralized cofactor solution of 20 mM NADP (nicotinamide adenine dinucleotide phosphate), and 100 mM sodium isocitrate in PBS.

Stannous chloride was dissolved in DMSO, which also served as the solvent control. The assay consisted of four solvent controls, three positive controls, and 5 or 6 concentrations of the test substance in duplicate or triplicate cultures. Tests were performed both with and without a metabolic activation system. The positive control was MMS (methyl methanesulfonate, 5 nl/ml) for tests without S9, and the positive control for tests with S9 was MCA (3-methylcholanthrene, 2.5 ug/ml).

6x 10e6 cells from THMG-treated stock cultures were seeded into 50-ml centrifuge tubes and resuspended in Fisher's treatment medium. The final volume was 10 ml after the addition of S9 mix. Tubes were sealed and placed on a roller drum (10-15 rpm) for 4 hours at 37 deg. C. After treatment, cells were centrifuged and the supernatant removed. Cells were then washed twice by resuspension and centrifugation in fresh growth medium, and resuspended in 20 ml of Fisher's or RPMI 1640 growth medium to obtain cell densities of 3 x 10e5 cells/ml. Cultures were returned to the roller drum for 48 hours to allow for expression and cell growth.

Cells were counted using an electronic counter, modified to allow colonies as small as 0.2 mm to be scored. The numbers of colonies in small and large classes of TFT-resistant mutants were calculated. Relative total growth, cloning efficiency, and mutant frequency (MF) were calculated. Statistical analyses were performed using a computer program for both the MF trend and for comparisons between each dose level and the solvent control.

Result : Stannous chloride was not mutagenic to L5178Y mouse lymphoma cells. The lowest average relative total growth values ranged from 30-35% without S9 to ~60% with S9. A precipitate formed at 80 ug/ml and there was a slight acidic pH shift in the medium at concentrations >=50 ug/ml.
Source : Myhr and Caspary. 1991
Test substance : Tin Dichloride [CAS No. 7772-99-8]; purity not reported, source: National Toxicology Program Chemical Repository.
Reliability : (2) valid with restrictions
Guideline study. Raw data are provided, but text was not readable in document reviewed (font was too small).

19.11.2003 (22)

Type : other: Transformation assay
System of testing : BALB/c-3T3 cells
Test concentration : 0 - 0.0633 mM
Cycotoxic concentr. :
Metabolic activation : without
Result : negative
Method : other: Kukunaga (modified)
Year : 1973
GLP : no data
Test substance : other TS

Method : Each transformation assay contained three components: standard clonal survival assay, co-culture clonal survival assays, and a transformation assay.

Transformation was detected in 18-20 vessels/dose seeded with 3.2 x 10e4 cells/vessel. Various dose levels of the test substance were applied to triplicate cell cultures for 48 h, 2-4 days after seeding. After an 8-day

culture period, vessels were washed, fixed in methanol, stained with Giemsa, and colonies were counted. Stannous chloride was tested at four treatment doses in 2 or more independent assays. The dose levels covered a range of cytotoxic responses of approximately 10-100% relative cloning efficiency. The solvent used was DMSO and culture medium.

A test chemical had one of four possible transformation responses: sufficient positive, limited activity, sufficient negative, and limited negative. The number of type I-III transformed loci of BALB/c-3T3 cells were identified microscopically based on established criteria. Type III foci had 3 phenotypic properties: piling and overlapping cells, disorientation of cells at the periphery of the focus, and invasion of transformed cells into a contact-inhibited monolayer of wild-type cells. Type I and II foci lacked one or more of the 3 phenotypic properties of Type III transformed foci.

The statistical weighting procedure used mean and rank t-statistics. The significance of transformation responses was evaluated using analysis of variance and modified Student's t-tests. All statistical evaluations were performed using SAS software.

Result : Results of the standard clonal survival assay, by test trial and treatment condition:
Trial 1:
B(a)P 0.000791 mM = 0% relative cloning efficiency (RCE)
B(a)P 0.000250 mM = 1.67% RCE
Control = 100% RCE
Stannous chloride 0.015 mM = 75.0% RCE
Stannous chloride 0.0211 mM = 47.9% RCE
Stannous chloride 0.0422 mM = 7.08% RCE
Stannous chloride 0.0633 mM = 0% RCE

Trial 2:
B(a)P 0.000791 mM = 0.382% relative cloning efficiency (RCE)
B(a)P 0.000250 mM = 1.15% RCE
Control = 100% RCE
Stannous chloride 0.00659 mM = 78.2% RCE
Stannous chloride 0.0132 mM = 58.8% RCE
Stannous chloride 0.0264 mM = 26.3% RCE
Stannous chloride 0.0527mM = 3.82% RCE

Results of the co-culture clonal survival assay, by test trial and treatment condition:
Trial 1:
B(a)P 0.000791 mM = 62.5% relative cloning efficiency (RCE)
B(a)P 0.000250 mM = 89.0% RCE
Control = 100% RCE
Stannous chloride 0.015 mM = 93.0% RCE
Stannous chloride 0.0211 mM = 72.4% RCE
Stannous chloride 0.0422 mM = 29.6% RCE
Stannous chloride 0.0633 mM = 9.19% RCE

Trial 2:
B(a)P 0.000791 mM = 13.5% relative cloning efficiency (RCE)
B(a)P 0.000250 mM = 56.2% RCE
Control = 100% RCE
Stannous chloride 0.00659 mM = 68.2% RCE
Stannous chloride 0.0132 mM = 56.9% RCE
Stannous chloride 0.0264 mM = 69.7% RCE

Stannous chloride 0.0527mM = 33.6% RC

Transforming activity, expressed as the number of Type III foci >2mm in diameter/culture vessel, by test trial and treatment condition:
Trial 1:
B(a)P 0.000791 mM = 99
B(a)P 0.000250 mM = 100
Control = 18
Stannous chloride 0.015 mM = 11
Stannous chloride 0.0211 mM = 10
Stannous chloride 0.0422 mM = 9
Stannous chloride 0.0633 mM = 11

Trial 2:
B(a)P 0.000791 mM = 204
B(a)P 0.000250 mM = 144
Control = 46
Stannous chloride 0.00659 mM = 25
Stannous chloride 0.0132 mM = 39
Stannous chloride 0.0264 mM = 35
Stannous chloride 0.0527mM = 28

Transformation responses, expressed as Type III foci/vessel, by test trial and treatment condition:
Trial 1:
B(a)P 0.000791 mM = 4.61*
B(a)P 0.000250 mM = 4.02*
Control = 0.357
Stannous chloride 0.015 mM = 0.423
Stannous chloride 0.0211 mM = 0.266
Stannous chloride 0.0422 mM = 0.327
Stannous chloride 0.0633 mM = 0.402

Trial 2:
B(a)P 0.000791 mM = 9.88*
B(a)P 0.000250 mM = 6.58*
Control = 0.907
Stannous chloride 0.00659 mM = 1.04
Stannous chloride 0.0132 mM = 1.61*
Stannous chloride 0.0264 mM = 1.45
Stannous chloride 0.0527mM = 1.18

* = significant

Stannous chloride was inactive in the transformation assay and was cytotoxic to BALB/c-3T3 cells, with an average LD50 for the cytotoxic response of 0.0285 mM. Stannous chloride was identified as a "level E non-carcinogen", i.e., equivocal evidence of carcinogenic activity.

Source : Matthews et al. 1993
Test substance : Tin Dichloride [CAS No. 7772-99-8]; solid, source: Radian Corporation, Houston, TX.
Reliability : (2) valid with restrictions
Non-guideline study. Characterization of test substance not reported.

19.11.2003 (20)

Type : Cytogenetic assay
System of testing : Human embryonic lung cultures (WI-38)

Test concentration	:	0, 0.1, 1.0, 10.0 mcg/ml
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method :

Human embryonic lung cultures (WI-38) free of viruses and mycoplasm were used. Cells were suspended in tissue culture medium (2 x 10e6 cells/ml) [minimal essential medium + 1% glutamine + 200 units/ml penicillin + 200 ug/ml streptomycin + 15% fetal calf serum] and "planted" in dilution bottles at a concentration of 5 x 10e5 cells/ml. 24-h later, the test substance was added at three dose levels (0.1, 1.0, and 10.0 mcg/ml), using 3 bottles per dose level.

Cells were incubated at 37 deg. C and were examined twice daily for 3 days to determine whether an adequate number of mitoses were present. Cells were harvested when sufficient mitoses were observed, usually 24-48 h after planting. At harvest, cells were centrifuged and fixed in absolute methanol:glacial acetic acid (3:1) for 30 minutes, then re-centrifuged, decanted, and suspended in 2% acetic acid-orcein stain, dropped onto slides, and examined.
The positive control was triethylene melamine (TEM, 0.1 mcg/ml dissolved in saline). The negative control was 0.85% saline.

Anaphase preparations were examined. Cytopathic effects or inhibition of mitoses were scored as toxicity. Results were reported as (1) percentage of cells in mitosis (200 cells/dose level), (2) percentage of cells with acentric fragments, (3) percentage of cells with bridges, (4) percentage of multipolar cells, (5) percentage of cells with other aberrations (i.e., polyploidy, pulverization, fragments, or >10 aberrations), and (6) percentage of cells with duplicate aberrations in a single cell.

Result :

Negative saline control: % cells in mitosis = 3; % cells with acentric fragments = 0; % cells with bridges = 0; % multipolar cells = 0; % cells with other aberrations = 0; % cells with duplicate aberrations = 0

Positive TEM control: : % cells in mitosis = 1; % cells with acentric fragments = 12; % cells with bridges = 6; % multipolar cells = 6; % cells with other aberrations = 0; % cells with duplicate aberrations = 24

0.1 mc/ml: : % cells in mitosis = 1; % cells with acentric fragments = 0; % cells with bridges = 0; % multipolar cells = 0; % cells with other aberrations = 0; % cells with duplicate aberrations = 0

1.0 mcg/ml: : % cells in mitosis = 2; % cells with acentric fragments = 0; % cells with bridges = 0; % multipolar cells = 0; % cells with other aberrations = 0; % cells with duplicate aberrations = 0

10.0 mcg/ml: : % cells in mitosis = 2; % cells with acentric fragments = 4; % cells with bridges = 1; % multipolar cells = 0; % cells with other aberrations = 0; % cells with duplicate aberrations = 5

The authors reported that the positive control produced a significantly higher percentage of aberrations on the chromosomes relative to the negative control or the test substance. The negative control was within

normal limits. Stannous chloride "produced no significant aberration in the anaphase chromosomes of human tissue culture cells when tested at the dosage levels employed in this study."

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.
Reliability : (2) valid with restrictions
Study predates GLP. No information on test substance purity.

20.11.2003 (18)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period :
Doses : 0 and 1300 mg/kg
Result : negative
Method : other: not reported
Year :
GLP : no
Test substance : other TS

Method : Random-bred male albino rats (10-12 weeks old) were obtained from a closed colony. The test substance was administered via gavage at a dose of 1300 mg/kg in an acute study. The negative control was saline. The positive control was triethylene melamine (TEM, 0.3 mg/kg). The positive control substance was administered by i.p. injection.

At a dose of 1300 mg/kg, 15 rats were tested with 5 animals each sacrificed at 6, 24, and 48 hours post dose administration. In the negative (saline) control, the test was initiated with a total of 9 animals, with 3 animals sacrificed at 6, 24, and 48 h post administration. In the positive (TEM) control, a total of 5 animals were tested; all 5 were sacrificed 24 h post dose administration.

4 h after the last dose was administered and 2 h prior to sacrifice, each animal was administered 4 mg/kg colcemide by i.p. injection to arrest C-mitosis in bone marrow cells. Bone marrow samples were removed, aspirated into 5 ml Hanks' balanced salt solution in a capped test tube, centrifuged at 1500 rpm for 5 minutes, and decanted. 2 ml of hypotonic 0.5% KCl solution was added to each tube; tubes were gently agitated to resuspend cells. Tubes were placed in a 37 deg. C water bath for 20 minutes, then centrifuged at 1500 rpm for 5 minutes, decanted, and fixed with 2 ml absolute methanol:glacial acetic acid (3:1). Cells were resuspended in the fixative, gently agitated, and the capped tubes were incubated at 4 deg. C for 30 minutes. Samples were then centrifuged, decanted, and 2 ml of fixative added. Cells were resuspended and incubated at 4 deg. C overnight. Following overnight incubation, the samples were centrifuged, decanted, and 0.3-0.6 ml of fresh fixative added. Cells were resuspended and 2-3 drops of the suspension were placed on clean, dry slides held 15 deg. From horizontal to allow the suspension to flow to the edge of the slide. Slides were ignited by a alcohol burner and allowed to flame, then were air dried overnight at room temperature.

Duplicate slides were prepared of each treatment group. Slides were stained with 5% Giemsa, rinsed in acetone, then acetone:xylene (1:1), and then placed in xylene for 30 minutes. Slides were examined under the microscope and metaphase spreads were examined and counted.

The chromosomes of each cell were counted and diploid cells were analyzed. Cells were scored for chromatid gaps and breaks, chromosome gaps and breaks, reunions, cells with >10 aberrations, polyploidy, pulverization, and any other chromosomal aberrations observed. 50 metaphases were scored per animal. Mitotic indices were obtained by counting at least 500 cells and expressed as the ratio of the number of cells in mitosis/the number of cells observed.

Result : 1300 mg/kg: % cells in mitosis = 3.00 (6 h), 4.27 (24 h), 4.28 (48 h); number of cells with breaks = 0 at all time points; number of cells with reunions = 0 at all time points; number of cells with aberrations = 1 (6 h), 0 (24 h), 1 (48 h)

Negative control: % cells in mitosis = 4.47 (6 h), 3.47 (24 h), 5.73 (48 h); number of cells with breaks = 0 at all time points; number of cells with reunions = 29* (6 h), 0 (24 h), 0 (48 h); number of cells with aberrations = 29* (6 h), 0 (24 h), 0 (48 h)

*One animal exhibited an abnormally large metacentric chromosome and had a diploid number of 41. This was considered to be normal for this animal.

Positive control (24 h): % cells in mitosis = 1.06; number of cells with breaks = 3; number of cells with reunions = 58; number of cells with aberrations = 101

The authors reported that the neither the number or variety of aberrations in treatment cells differed significantly from the negative controls; therefore, stannous chloride was considered to be non-mutagenic under the conditions of the cytogenetic study.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.
Reliability : (2) valid with restrictions
Study predates GLP. Lacks information on environmental conditions of housing and feed and water consumption. No information on test substance purity.

20.11.2003 (18)

Type : Cytogenetic assay
Species : rat
Sex : male
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period :
Doses : 0, 4, 40, and 400 mg/kg
Result : negative
Method : other: not reported
Year :
GLP : no
Test substance : other TS

Method : Random-bred male albino rats (10-12 weeks old) were obtained from a

closed colony and used in acute and subacute cytogenetics studies. In the acute study, a total of 59 rats were used. In the subacute study, a total of 18 rats were used.

The positive control was triethylene melamine (TEM, 0.3 mg/kg). The negative control was saline. Dose levels of the test substance tested: 4, 40, and 400 mg/kg. The test substance was administered by gavage. The positive control substance was administered by i.p. injection.

ACUTE STUDY:
At dose levels of 4, 40, and 400 mg/kg, 15 rats were tested at each dose level with 5 animals from each group sacrificed at 6, 24, and 48 hours post dose administration. In the negative (saline) control, the test was initiated with a total of 9 animals, with 3 animals sacrificed at 6, 24, and 48 h post administration. In the positive (TEM) control, a total of 5 animals were tested; all 5 were sacrificed 48 h post dose administration.

SUBACUTE STUDY:
Five doses were administered 24 hours apart. At dose levels of 4, 40, and 400 mg/kg, 5 rats per group were tested and sacrificed 6 hours after the last dose was administered. In the negative (saline) control, a total of 3 animals were tested and sacrificed 6 hours after the last dose was administered. No positive control group was included.

4 h after the last dose was administered and 2 h prior to sacrifice, each animal was administered 4 mg/kg colcemide by i.p. injection to arrest C-mitosis in bone marrow cells. Bone marrow samples were removed, aspirated into 5 ml Hanks' balanced salt solution in a capped test tube, centrifuged at 1500 rpm for 5 minutes, and decanted. 2 ml of hypotonic 0.5% KCl solution was added to each tube; tubes were gently agitated to resuspend cells. Tubes were placed in a 37 deg. C water bath for 20 minutes, then centrifuged at 1500 rpm for 5 minutes, decanted, and fixed with 2 ml absolute methanol:glacial acetic acid (3:1). Cells were resuspended in the fixative, gently agitated, and the capped tubes were incubated at 4 deg. C for 30 minutes. Samples were then centrifuged, decanted, and 2 ml of fixative added. Cells were resuspended and incubated at 4 deg. C overnight. Following overnight incubation, the samples were centrifuged, decanted, and 0.3-0.6 ml of fresh fixative added. Cells were resuspended and 2-3 drops of the suspension were placed on clean, dry slides held 15 deg. From horizontal to allow the suspension to flow to the edge of the slide. Slides were ignited by a alcohol burner and allowed to flame, then were air dried overnight at room temperature. Duplicate slides were prepared of each treatment group. Slides were stained with 5% Giemsa, rinsed in acetone, then acetone:xylene (1:1), and then placed in xylene for 30 minutes. Slides were examined under the microscope and metaphase spreads were examined and counted.

The chromosomes of each cell were counted and diploid cells were analyzed. Cells were scored for chromatid gaps and breaks, chromosome gaps and breaks, reunions, cells with >10 aberrations, polyploidy, pulverization, and any other chromosomal aberrations observed. 50 metaphases were scored per animal. Mitotic indices were obtained by counting at least 500 cells and expressed as the ratio of the number of cells in mitosis/the number of cells observed.

Result : ACUTE STUDY (counts determined at 6, 24, and 48-h):
Negative control: % cells in mitosis = 15 (6 h), 10 (24 h), 15 (48 h); % cells with breaks = 0 at all time points; % cells with reunions = 0 at all time

points; % cells with aberrations = 0 at all time points

4 mg/kg: % cells in mitosis = 12 (6 h), 8 (24 h), 11 (48 h); % cells with breaks = 1 (6 h), 1 (24 h), 2 (48 h); % cells with reunions = 0 at all time points; % cells with aberrations = 1 (6 h), 1 (24 h), 2 (48 h)

40 mg/kg: % cells in mitosis = 9 (6 h), 12 (24 h), 16 (48 h); % cells with breaks = 1 (6 h), 1 (24 h), 0 (48 h); % cells with reunions = 0 at all time points; % cells with aberrations = 1 (6 h), 1 (24 h), 0 (48 h)

400 mg/kg: % cells in mitosis = 12 (6 h), 10 (24 h), 19 (48 h); % cells with breaks = 0 (6 h), 1 (24 h), 3 (48 h); % cells with reunions = 0 at all time points; % cells with aberrations = 0 (6 h), 1 (24 h), 3 (48 h)

Positive control (48 h): % cells in mitosis = 3; % cells with breaks = 30; % cells with reunions = 12; % cells with aberrations = 43

SUBACUTE STUDY (counts at 6 h):
Negative control: % cells in mitosis = 11; % cells with breaks = 0; % cells with reunions = 0; % cells with aberrations = 0

4 mg/kg: % cells in mitosis = 12; % cells with breaks = 2; % cells with reunions = 1; % cells with aberrations = 3

40 mg/kg: % cells in mitosis = 12; % cells with breaks = 3; % cells with reunions = 0; % cells with aberrations = 3

400 mg/kg: % cells in mitosis = 13; % cells with breaks = 3; % cells with reunions = 0; % cells with aberrations = 3

For the acute study, the authors reported that the chromosomal abnormalities observed in the positive controls were significantly higher than either the negative controls or the test substance. The maximum effect of the positive control was observed at 48 hours post administration. The percentage of breaks in the experimental groups was within normal ranges (1-3%).

For the subacute study, the authors reported that although the experimental groups contained breaks with a higher percentage than the negative control, values were within normal limits.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.
Reliability : (2) valid with restrictions
Study predates GLP. Lacks information on environmental conditions of housing and feed and water consumption. No information on test substance purity.

20.11.2003 (18)

Type : Dominant lethal assay
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : single dose
Doses : 0 and 1300 mg/kg
Result : negative

Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method :

Male and female Sprague-Dawley rats were obtained from a closed colony. At test initiation, animals were 10-12 weeks old.

The positive control was 0.3 mg/kg triethylenemelamine (TEM). The negative control was solvent (saline) only. A single dose level of the test substance was tested: 1300 mg/kg. The test substance and solvent control were administered by oral intubation; the positive control substance was administered by i.p. injection.

10 male rats were treated with a single dose of the test substance, solvent control, or positive control. Treated males were then mated to two untreated virgin female rats per week for 8 weeks. Females were sacrificed 14 days after separation from the males and the uterus was examined for corpora lutea, early/late fetal deaths and total implantations. Two independent tests were conducted.

Statistical analysis of the data were performed as follows:
Fertility index: number of pregnant females/number of mated females. Chi-square used to compare treatment groups to the control group. Armitage's trend used to test whether the fertility index was linearly related to the arithmetic or log dose.
Total number of implantations: differences between average number of implantations/pregnant female in each treatment group relative to the control group were evaluated by t-test.
Total number of corpora lutea: significant differences between treatment groups and the control determined by t-test.
Preimplantation loss: determined by subtracting the number of implantations from the number of corpora lutea. Preimplanation losses for each female were evaluated using the Freeman-Tukey transformation. Comparisons of treatment groups to the control group were by t-test.
One or more dead implants: each treatment compared to the control by chi-square test. Armitage's trend used to test whether proportions were linearly related to the arithmetic or log dose.

Result :

***Only results reported are statistically significant findings relative to the negative (solvent) control:

Fertility index: 1300 mg/kg, decreased Week 1.

Average number of implantations/pregnant female: Findings for positive control group only (Weeks 1-4, 6).

Average corpora lutea/pregnant female: Positive control group, decreased Weeks 1 and 2. 1300 mg/kg, decreased Week 5.

Average preimplanation losses/pregnant female: 1300 mg/kg, decreased Weeks 1, 3 and increased Week 4. Positive control, increased Weeks 2-4 and decreased Week 6.

Average resorptions/pregnant female: 1300 mg/kg, increased Weeks 6, 7. Positive control, increased Weeks 1-5, 7, 8.

Proportion of females with one or more dead implants: Positive control,

increased Weeks 1-7. 1300 mg/kg, increased Week 6.

Proportion of females with two or more dead implants: Positive control, increased Weeks 1-5, 8.

Proportion of dead implants/total implants: Positive control, increased Weeks 1-5, 7, 8. 1300 mg/kg, increased Weeks 6-8.

Based on the results of the studies conducted, no dose-related or time-related patterns were evident; therefore, the test compound was determined not to induce dominant lethal mutations.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.
Reliability : (2) valid with restrictions
Study predates GLP. Study lacks information on environmental conditions of housing, feed and water consumption and criteria used for scoring dominant lethals.

20.11.2003 (18)

Type : Dominant lethal assay
Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period :
Doses : 0, 4, 40, and 400 mg/kg
Result : negative
Method : other: not reported
Year :
GLP : no
Test substance : other TS

Method : Male and female Sprague-Dawley rats were obtained from a closed colony. At test initiation, animals were 10-12 weeks old. Animals were provided food and water ad libitum.

The positive control was 0.3 mg/kg triethylenemelamine (TEM). The negative control was solvent (saline) only. Dose levels of the test substance were 4, 40, and 400 mg/kg. The test substance and solvent control were administered by oral intubation; the positive control substance was administered by i.p. injection.

Two tests were conducted; an acute study and a subacute study. In the acute study, male rats (10/group) were treated once with a single dose of the test substance, solvent control, or positive control, then mated to two untreated virgin female rats per week for 8 weeks. In the subacute study, male rats (10/group) were treated once per day for 5 days then mated to two untreated virgin female rats per week for 7 weeks.

Females were sacrificed 14 days after separation from the males and the uterus was examined for corpora lutea, early/late fetal deaths and total implantations. A ositive control group was not included in the subacute test.

Statistical analysis of the data were performed as follows:
Fertility index: number of pregnant females/number of mated females.

Chi-square used to compare treatment groups to the control group.
Armitage's trend used to test whether the fertility index was linearly related to the arithmetic or log dose.
Total number of implantations: differences between average number of implantations/pregnant female in each treatment group relative to the control group were evaluated by t-test.
Total number of corpora lutea: significant differences between treatment groups and the control determined by t-test.
Preimplantation loss: determined by subtracting the number of implantations from the number of corpora lutea. Preimplanation losses for each female were evaluated using the Freeman-Tukey transformation. Comparisons of treatment groups to the control group were by t-test.
One or more dead implants: each treatment compared to the control by chi-square test. Armitage's trend used to test whether proportions were linearly related to the arithmetic or log dose.

Result : ***Only results reported are statistically significant findings relative to the negative (solvent) control:

Fertility index:
Subacute study: 4 mg/kg, increased Week 3 and decreased Week 7. 40 mg/kg, decreased Week 7.
Acute study: 40 mg/kg, increased Weeks 3, 6. Positive control, increased Week 6. 400 mg/kg; decrease Week 7.

Average number of implantations/pregnant female:
Subacute study: 4 and 40 mg/kg, increased Week 6.
Acute study: Positive control, decreased Weeks 1-4, 6. 4 mg/kg, increased Week 6. 400 mg/kg, decreased Week 3. All dose levels and positive control, decreased Week 7.

Average corpora lutea/pregnant female:
Subacute study: 4 mg/kg, decreased Week 2. All dose levels increased Week 6.
Acute study: Positive control, decreased Weeks 1, 3, 4, 6. 4 mg/kg, increased Week 6; decreased Week 8. 40 mg/kg, increased Week 6; decreased Week 8. 400 mg/kg, decreased Weeks 3, 8; increased Week 6.

Average preimplanation losses/pregnant female:
Subacute study: 4 mg/kg, increased Weeks 3, 5, 6. 40 mg/kg, increased Weeks 3, 6, 7. 400 mg/kg, increased Weeks 3, 6.
Acute study: Positive control, increased Weeks 1-3, 7; decreased Week 8. 4 and 40 mg/kg, increased Week 7; decreased Week 8. 400 mg/kg, increased Week 6, 7; decreased Week 8.

Average resorptions/pregnant female:
Subacute study: 4 mg/kg, increased Week 6. 40 and 400 mg/kg, increased Week 3.
Acute study: Positive control, increased Weeks 1, 2, 4, 6. 4 and 400 mg/kg, increased Week 7.

Proportion of females with one or more or two or more dead implants:
Subacute study: No findings.
Acute study: Findings for positive control group only.

Proportion of dead implants/total implants:
Subacute study: 40 and 400 mg/kg, increased Week 3.
Acute study: Positive control, findings for Weeks 1-7. 4, 40, 400 mg/kg,

increased Week 7.

Based on the results of the studies conducted, no dose-related or time-related patterns were evident; therefore, the test compound was determined not to induce dominant lethal mutations.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.
Reliability : (2) valid with restrictions
Study predates GLP. Study lacks information on environmental conditions of housing, feed and water consumption and criteria used for scoring dominant lethals.

20.11.2003 (18)

Type : Micronucleus assay
Species : mouse
Sex : male
Strain : B6C3F1
Route of admin. : i.p.
Exposure period : single injection x 3 consecutive days; sacrifice at 48-h after last injection
Doses : 0, 26.3, 52.5, 105 mg/kg
Result : negative
Method : other: not reported
Year :
GLP : no data
Test substance : other TS

Method : Male B6C3F1 mice (9-14 weeks old) were obtained from the National Toxicology Program. Animals had an initial body weight range of 25-33 g.

Stannous chloride was prepared in either phosphate buffered saline or corn oil. The test substance was administered by intraperitoneal (IP) injection at a volume of 0.4 ml/mouse to groups of 5 mice/dose level on 3 consecutive days. Animals were monitored twice daily. 48h following the 3rd and last injection, surviving animals were sacrificed. Bone marrow (2 slides/tissue/mouse) was prepared by direct technique. Smears were air dried, fixed in methanol, and stained with acridine orange.

Dose levels tested: 0, 26.3, 52.5, 105 mg/kg. A repeat test was conducted to 210 mg/kg. Positive control was 7,12-dimethylbenzanthracene or mitomycin. Negative control was solvent used (phosphate buffered saline or corn oil).

Slides were examined at 1,000x magnification. The number of micronucleated polychromatic erythrocytes (MN-PCE) among 2,000 PCE and the percentage of PCE among 200 erythrocytes were determined.

Data were analyzed using the Micronucleus Assay Data Management and Statistical software package (v1.4). The level of significance was 0.05. A one-tailed trend test was used to analyze the number of MN-PCE, which were pooled within each dose group. Percent PCE data were evaluated by analysis of variance based on pooled data. An unadjusted one-tailed Pearson chi-square test was used for pairwise comparisons between each group and the concurrent solvent control.

Result : Micronucleated PCEs per 1000 PCE scored, by dose level tested:
Control (0 mg/kg): 3.70 ± 0.58
26.3 mg/kg: 2.38 ± 0.38

52.5 mg/kg: 1.60 ± 0.19
105 mg/kg: 2.40 ± 0.37

Percent PCE, by dose level tested:
Control (0 mg/kg): 57.8
26.3 mg/kg: 43.5
52.5 mg/kg: 45.9
105 mg/kg: 39.8

All animals in each group survived (5/5) at dose levels of 0, 52.5, and 105 mg/kg. A single animal died in the 26.3 mg/kg dose group.

Under the experimental conditions, there is no evidence that stannous chloride produced an increase in the number of micronucleated polychromatic erythrocytes in male B6C3F1 mice. In the repeat study, stannous chloride did not produce an increase in the micronucleated polychromatic erythrocytes at dose levels up to 210 mg/kg.

Source : Shelby et al. 1993
Test substance : Tin Dichloride [CAS No. 7772-99-8]; purity not reported, source: National Toxicology Program Chemical Repository.
Reliability : (2) valid with restrictions
Guideline study without detailed documentation.

19.11.2003 (25)

Type : Somatic mutation assay
Species : Drosophila melanogaster
Sex : male/female
Strain : other: mwh (multiple wing hairs) and flr3/TM3, Ser.
Route of admin. : oral feed
Exposure period : 48 hours
Doses : 50 and 100 mM
Result : negative
Method : other: Wing Spot Test (Graf et al.)
Year : 1984
GLP : no data
Test substance : other TS

Method : The genotoxicity of stannous chloride was tested using Drosophila melanogaster per the method described in Graf et al. (1984).

Outcrossed stock organisms: mwh (multiple wing hairs) and flr3/TM3, Ser. 72 +/1 4h old larvae were used for test initiation. 50-100 larvae were transferred to plastic vials containing 1.6 g instant medium. The test substance was added to the medium, resulting in final test concentrations of 50 and 100 mM of stannous chloride.

Stannous chloride solutions were prepared in 5 ml of 0.03N HCl. The solvent was used as the negative control. Two independent assays were performed.

Statistical analysis of the data was performed based on the method described by Frei and Wurgler (1988). If there were no statistical differences between the results of the independent assays, the data were pooled.

Result : Results of the Drosophila wing spot test of stannous chloride, by concentration tested:

Number of wings:
Control: 80
50 mM: 80
100 mM: 58

Spots per wing:
Control: 0.36 small single, 0.04 large single, 0.01 twin, 0.41 total spots
50 mM: 0.25 small single, 0.06 large single, 0.00 twin, 0.31 total spots
100 mM: 0.34 small single, 0.07 large single, 0.00 twin, 0.41 total spots

Spots with mwh clone:
Control: 32
50 mM: 25
100 mM: 24

Mean number of cell division cycles:
Control: 1.78
50 mM: 1.64
100 mM: 2.00

Frequency of clone formation observed (x10e-5)
Control: 1.6
50 mM: 1.3
100 mM: 1.7

Stannous chloride, tested at 50 and 100 mM was negative for the induction of small single spots and inconclusive for the induction of large single and twin spots.

Source : Tripathy et al. 1990
Test substance : Tin Dichloride [CAS No. 7772-99-8]; source: Fluka.
Reliability : (2) valid with restrictions
Similar to guideline study without detailed documentation. Purity of test substance not reported. No positive control reported.

17.11.2003 (27)

Type : other: Host-mediated assay
Species : mouse
Sex : male
Strain : ICR
Route of admin. : gavage
Exposure period :
Doses : 0, 4, 40, and 400 mg/kg
Result : negative
Method : other: not reported
Year :
GLP : no
Test substance : other TS

Method : Male ICR mice were obtained from Flow Laboratories. In acute and subacute tests, 10 male mice (25-30 g each) were evaluated at each dose level of the test substance (4, 40, and 400 mg/kg), with the negative (solvent) control, and with the positive controls: dimethyl nitrosamine (DMN, 100 mg/kg) for the assays with Salmonella, and ethylmethane sulfonate (EMS, 350 mg/kg) for the assay with Saccharomyces.

The indicator organism used to evaluate the induction of reverse mutations was Salmonella typhimurium (strains TA1530 and his G-46). Salmonella

were cultured in tryptone yeast extract gel and transferred weekly. 48-h prior to use, Salmonella were transferred to tryptone yeast extract broth, then transferred to fresh broth at 24 h and again at 8 h prior to testing. The mouse inoculum was prepared by transferring 4-ml of the 8-h Salmonella/tryptone yeast extract broth to 50-ml bottles. Exponential log-phase organisms were inoculated into mice by i.p. injection (2 ml) when the approximate cell density reached 3.0 x 10e8 cells/ml. Doses of the test substance were administered to mice by gavage. Tenfold dilutions were made of each peritoneal exudate (0.5 ml exudates + 4.5 ml saline), resulting in final concentrations ranging from 10e0 (undiluted peritoneal exudates) through 10e-7. 0.2 ml of the 10e-6 and 10e-7 dilutions were plated on tryptone yeast extract agar for determination of total bacterial counts (3 plates/sample). For total mutant counts, 0.2 ml of the 10e0 dilution was spread over minimal agar plates (5 plates). Plates were incubated at 37 deg C. for 18 h for the tryptone yeast extract agar plates and 40 h for the minimal agar plates.

The indicator organism used to evaluate mitotic recombination was Saccharomyces cerevisiae. Ten fold dilutions (10e0 to 10e-5) were made of each sample. 0.1 ml of the 10e-5, 10e-4, and 10e-3 dilutions were placed on complete medium (10 plates/dilution). Plates were incubated for 40 h at 30 deg. C. The 10e-5 dilutions were used to determine total populations. The 10e-4 and 10e-3 dilutions were examined after an additional incubation of 40 h at 4 deg. C for red sectors indicating a mutation.

In the acute study, animals were sacrificed 3 h post-dosing and 2 ml of sterile saline solution was injected i.p. into each mouse. Fluid was removed aseptically from the peritoneal cavity.

In the subacute study, groups of mice (10/treatment) received five oral doses of the test substance 24 h apart. 30 minutes following the last dose administered, mice were inoculated with the indicator organism then sacrificed.

Result : Results (mean values) reported for the Acute and Subacute host-mediated assays: total colony forming units (CFU x 10e8/1.0 ml), total number of mutants (x 10e0/1.0 ml), and the mutation frequency (x 10e-8) are reported for each dose and control group tested, and by Salmonella indicator strain.

Salmonella strain TA1530 - Acute assay
Negative saline control: 4.63 CFU, 2.80 total mutants, 0.67 mutation frequency
Positive DMN control: 5.13 CFU, 35.37 total mutants, 6.92 mutation frequency
4 mg/kg: 3.29 CFU, 4.25 total mutants, 1.21 mutation frequency
40 mg/kg: 4.70 CFU, 3.86 total mutants, 0.37 mutation frequency
400 mg/kg: 4.61 CFU, 3.56 total mutants, 0.70 mutation frequency

Salmonella strain TA1530 - Subacute assay
4 mg/kg: 24.1 CFU, 28.1 total mutants, 1.19 mutation frequency
40 mg/kg: 4.83 CFU, 5.25 total mutants, 0.96 mutation frequency
400 mg/kg: 4.38 CFU, 20.5 total mutants, 5.52 mutation frequency

Salmonella strain G46 - Acute assay
Negative saline control: 7.98 CFU, 7.12 total mutants, 0.90 mutation frequency
Positive DMN control: 3.58 CFU, 109.89 total mutants, 36.59 mutation

frequency
4 mg/kg: 6.24 CFU, 14.43 total mutants, 2.39 mutation frequency
40 mg/kg: 5.92 CFU, 20.75 total mutants, 3.50 mutation frequency
400 mg/kg: 9.45 CFU, 17.22 total mutants, 1.83 mutation frequency

Salmonella strain G46 - Subacute assay
4 mg/kg: 4.90 CFU, 17.60 total mutants, 3.22 mutation frequency
40 mg/kg: 6.67 CFU, 15.30 total mutants, 2.80 mutation frequency
400 mg/kg: 6.58 CFU, 21.90 total mutants, 3.26 mutation frequency

Saccharomyces strain D3 - Acute assay
Negative saline control: 0.29 CFU, 1.70 total mutants, 6.72 mutation frequency
Positive EMS control: 0.39 CFU, 20.8 total mutants, 57.54 mutation frequency
4 mg/kg: 0.14 CFU, 1.73 total mutants, 7.79 mutation frequency
40 mg/kg: 0.28 CFU, 1.33 total mutants, 4.68 mutation frequency
400 mg/kg: 0.18 CFU, 1.7 total mutants, 3.49 mutation frequency

Saccharomyces strain D3 - Subacute assay
Negative saline control: 0.27 CFU, 1.20 total mutants, 3.94 mutation frequency
4 mg/kg: 0.27 CFU, 1.11 total mutants, 3.73 mutation frequency
40 mg/kg: 0.26 CFU, 1.5 total mutants, 4.32 mutation frequency
400 mg/kg: 0.25 CFU, 2.63 total mutants, 9.58 mutation frequency

All assays with Saccharomyces cerevisiae strain D3 and Salmonella typhimurium strain G46 were negative. In the subacute assays with Salmonella typhimurium strain TA1530, there was an elevated frequency at the 400 mg/kg level. The authors noted that this increased frequency may be real or possibly the result of high mutant counts for two of the 10 test animals.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.
Reliability : (2) valid with restrictions
Study predates GLP. Lacks information on environmental conditions of housing and feed and water consumption. No information on test substance purity.

20.11.2003 (18)

Type : other: Host-mediated assay
Species : mouse
Sex : male
Strain : ICR
Route of admin. : gavage
Exposure period :
Doses : 0 and 1300 mg/kg
Result : negative
Method : other: not reported
Year :

GLP : no
Test substance : other TS

Method : Male ICR mice were obtained from Flow Laboratories. In acute and subacute tests, 10 male mice (25-30 g each) were evaluated at a dose level of 1300 mg/kg test substance, with the negative (solvent) control, and with the positive controls: dimethyl nitrosamine (DMN, 100 mg/kg) for the assays with Salmonella, and ethylmethane sulfonate (EMS, 350 mg/kg) for the assay with Saccharomyces.

The indicator organism used to evaluate the induction of reverse mutations was Salmonella typhimurium (strains TA1530 and G-46). Salmonella were cultured in tryptone yeast extract gel and transferred weekly. 48-h prior to use, Salmonella were transferred to tryptone yeast extract broth, then transferred to fresh broth 24 h and again at 8 h prior to testing. The mouse inoculum was prepared by transferring 4-ml of the 8-h Salmonella/tryptone yeast extract broth to 50-ml bottles. Exponential log-phase organisms were inoculated into mice by i.p. injection (2 ml) when cell density reached 3.0 x 10e8 cells/ml. Doses of the test substance were administered to mice by gavage. Tenfold dilutions were made of each peritoneal exudate (0.5 ml exudates + 4.5 ml saline), resulting in final concentrations ranging from 10e0 (undiluted peritoneal exudates) through 10e-7. 0.2 ml of the 10e-6 and 10e-7 dilutions were plated on tryptone yeast extract agar for determination of total bacterial counts (3 plates/sample). For total mutant counts, 0.2 ml of the 10e0 dilution was spread over minimal agar plates (5 plates). Plates were incubated at 37 deg C. for 18 h for the tryptone yeast extract agar plates and 40 h for the minimal agar plates.

The indicator organism used to evaluate mitotic recombination was Saccharomyces cerevisiae. Ten fold dilutions (10e0 to 10e-5) were made of each sample. 0.1 ml of the 10e-5, 10e-4, and 10e-3 dilutions were placed on complete medium (10 plates/dilution). Plates were incubated for 40 h at 30 deg. C. The 10e-5 dilutions were used to determine total populations. The 10e-4 and 10e-3 dilutions were examined after an additional incubation of 40 h at 4 deg. C for red sectors indicating a mutation.

In the acute study, animals were sacrificed 3 h post-dosing and 2 ml of sterile saline solution was injected i.p. into each mouse. Fluid was removed aseptically from the peritoneal cavity.

In the subacute study, groups of mice (10/treatment) received five oral doses of the test substance 24 h apart. 30 minutes following the last dose administered, mice were inoculated with the indicator organism then sacrificed.

Result : Results (mean values) reported for the Acute and Subacute host-mediated assays: total colony forming units (CFU x 10e8/1.0 ml), total number of mutants (x 10e0/1.0 ml), and the mutation frequency (x 10e-8) are reported for each dose and control group tested, and by Salmonella indicator strain.

Salmonella strain TA1530 - Subacute assay
Negative saline control: 6.01 CFU, 33.00 total mutants, 5.57 mutation frequency

Salmonella strain G46 - Subacute assay
Negative saline control: 6.13 CFU, 8.86 total mutants, 1.16 mutation frequency

Saccharomyces strain D3 - Subacute assay
Negative saline control: 1.61 CFU, 16.60 total mutants, 10.26 mutation frequency

Salmonella strain TA1530 - Acute assay
Positive DMN control: 6.09 CFU, 206.44 total mutants, 34.04 mutation frequency
1300 mg/kg: 7.06 CFU, 32.56 total mutants, 4.70 mutation frequency

Salmonella strain G46 - Acute assay
Positive DMN control: 9 CFU, 71.89 total mutants, 88.28 mutation frequency
1300 mg/kg: 6.72 CFU, 6.5 total mutants, 1.44 mutation frequency

Saccharomyces strain D3 - Acute assay
Positive EMS control: 1.17 CFU, 106.14 total mutants, 99.89 mutation frequency
1300 mg/kg: 1.27 CFU, 13.88 total mutants, 16.44 mutation frequency

All assays with Saccharomyces cerevisiae strain D3 and Salmonella typhimurium strains TA1530 and G46 were negative.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; crystal, source: Food and Drug Administration.
Reliability : (2) valid with restrictions
Study predates GLP. Lacks information on environmental conditions of housing and feed and water consumption. No information on test substance purity.

20.11.2003 (18)

5.7 CARCINOGENICITY

Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 105 weeks
Frequency of treatm. : ad libitum
Post exposure period :
Doses : 1000 and 2000 ppm
Result : negative
Control group : yes, concurrent no treatment
Method : other: NTP protocol
Year :
GLP : no data
Test substance : other TS

Method : Male and female F344/N rats (6 weeks old at time of study) were obtained from Frederick Cancer Research Center, Frederick, MD, USA, and acclimated to laboratory conditions for 10 days prior to test initiation.

Test groups:
50 male/50 female rats administered 2000 ppm stannous chloride in diet

50 male/50 female rats administered 1000 ppm stannous chloride in diet
50 male/50 female rats administered undosed (control) diet

Test diets contained 0, 1000 or 2000 ppm stannous chloride. Animals were caged in groups of 5, and dosed feed, control feed, and water were provided ad libitum. Environmental conditions of housing: temperature,19-24 deg. C; relative humidity, 30-70%; and photoperiod, 12-h light/12-h dark. Test diets were prepared and stored for up to 14 days. Stannous chloride in oral feed was found to be stable for two weeks at temperatures up to 25 deg. C. The concentration of stannous chloride in test diets was determined by Flame-AAS.

Animals were observed twice daily for mortality and morbidity. Clinical signs were recorded monthly. Body weights and feed consumption were recorded on an approximate monthly basis. Necropsies were performed on all animals at time of death or at the end of the 105-week study period.

Examinations for visible lesions were performed on all major tissues and organs. Microscopic examinations were performed on the following: all tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord.

The dose-related effect on survival was evaluated by the method of Cox (1972) for testing two groups and Tarone's (1975) method for testing for a dose-related trend. The incidence of neoplastic or nonneoplasic lesions was determined as the ratio of the number of animals with such lesions at a specific anatomic site to the number of animals in which that site was examined. Tumor incidence data were evaluated using pairwise comparisons (Fisher Exact Test) of high- and low-dosed groups with controls and tests for overall dose-response trends (Cochran-Armitage Linear Trend Test).

Result **:** MORTALITY AND TIME TO DEATH: No statistically significant differences. In male rats, 74% (37/50) of controls, 78% (39/50) of the low dose group, and 60% (30/50) of the high dose group survived to the end of the 105 week study period. In female rats, 84% (42/50) of controls, 78% (39/50) of the low dose group, and 72% (36/50) of the high dose group survived to the end of the 104-105 week study period.

One control male, 1 high-dose male, 1 low-dose female, and 2 high-dose females died during weeks 104-105 of natural causes.

CLINICAL SIGNS: No compound-related clinical signs observed.

BODY WEIGHT GAIN: Comparable to control group.

FEED/WATER CONSUMPTION: Comparable to control group. Average daily feed consumption per rat by low- and high-dose rats was 102% and 105%, respectively, of controls for males, and 98% and 95%, respectively, for females.

OPHTALMOSCOPIC EXAMINATION: Increased incidence of retinal degeneration was observed in high-dose males and low-dose females -

16% (8/50) in male control animals, 8% (4/50) in low-dose males, and 60% (30/50) in high-dose males; 4% (2/50) in female control animals, 74% (37/50) in low-dose females, and 6% (3/50) in high-dose females.

NEOPLASM FORMATION: Adenomas in the lungs of male rats showed a statistically significant (P<0.05) trend (0% (0/50) control, 0% (0/50) low-dose, 6% (3/50) high-dose); however, the statistical results of tests of the incidence of animals with either adenomas or carcinomas of the lung were not significant. No significant results occurred in female rats.

A positive trend in the incidence of male rats with C-cell adenoma or carcinoma in the thyroid and a significantly higher proportion in each dosed group was observed, relative to the controls (4% (2/50) control, 27% (13/49) low-dose, 16% (8/50) high-dose). C-cell adenomas were statistically significantly increased (P<0.05) in low-dose males. The C-cell tumor increase was not accompanied by a corresponding increased incidence of hyperplasia in the C-cells. Females had decreased proportions of C-cell adenomas or carcinomas in the high-dose group, relative to the controls.

DISCUSSION: C-cell adenomas of the thyroid, C-cell adenomas and carcinomas combined, and adenomas of the lung in male rats occurred with statistically significant positive trends and/or with statistically significant increased incidences in the dose groups relative to the controls. However, when lung adenomas in male rats are combined with lung carcinomas, no statistical significance remains. Thyroid C-cell tumors in male rats in the high-dose group were not statistically significantly different from historical control rates.

Although there was evidence for thyroid tumors and lung adenomas in male rats, the authors and peer reviewers concluded that under the conditions of the study performed, stannous chloride was not carcinogenic for male or female F344/N rats. The incidence of C-cell tumors of the thyroid gland in male rats may have been associated with the administration of the test substance.

Source : NTP. 1982
Test substance : Tin Dichloride [CAS No. 7772-99-8]; anhydrous, food grade ~98.5% purity, source: M&T Chemicals, Inc.
Reliability : (1) valid without restriction
Guideline study.

20.11.2003 (23)

Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 105 weeks
Frequency of treatm. : ad libitum
Post exposure period :
Doses : 1000 and 2000 ppm
Result : negative
Control group : yes, concurrent no treatment
Method : other: NTP protocol
Year :
GLP : no data
Test substance : other TS

Method : Male and female B6C3F1/N mice (6 weeks old at time of study) were obtained from Frederick Cancer Research Center, Frederick, MD, USA, and acclimated to laboratory conditions for 10 days prior to test initiation.

Test groups:
50 male/50 female mice administered 2000 ppm stannous chloride in diet
50 male/50 female mice administered 1000 ppm stannous chloride in diet
50 male/50 female mice administered a control diet (without stannous chloride)

Test diets contained 0, 1000 or 2000 ppm stannous chloride. Animals were caged in groups of 5, and dosed feed, control feed, and water were provided ad libitum. Environmental conditions of housing: temperature,19-24 deg. C; relative humidity, 30-70%; and photoperiod, 12-h light/12-h dark. Test diets were prepared and stored for up to 14 days. Stannous chloride in oral feed was found to be stable for two weeks at temperatures up to 25 deg. C. The concentration of stannous chloride in test diets was determined by Flame-AAS.

Animals were observed twice daily for mortality and morbidity. Clinical signs were recorded monthly. Body weight and feed consumption were recorded on an approximate monthly basis. Necropsies were performed on all animals at time of death or at the end of the 105-week study period.

Examinations for visible lesions were performed on all major tissues and organs. Microscopic examinations were performed on the following: all tissue masses, abnormal lymph nodes, skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction, thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach, duodenum, jejunum, ileum, colon, mesenteric lymph nodes, liver, gallbladder, pancreas, spleen, kidneys, adrenals, urinary bladder, seminal vesicles/prostate/testes or ovaries/uterus, nasal cavity, brain, pituitary, and spinal cord.

The dose-related effect on survival was evaluated by the method of Cox (1972) for testing two groups and Tarone's (1975) method for testing for a dose-related trend. The incidence of neoplastic or nonneoplasic lesions was determined as the ratio of the number of animals with such lesions at a specific anatomic site to the number of animals in which that site was examined. Tumor incidence data were evaluated using pairwise comparisons (Fisher Exact Test) of high- and low-dosed groups with controls and tests for overall dose-response trends (Cochran-Armitage Linear Trend Test).

Result : MORTALITY AND TIME TO DEATH: Statistically significant reduction ($P<0.05$) in survival of the male mouse control group relative to treated males of the low- and high-dose groups. In male mice, 64% (32/50) of controls, 84% (42/50) of the low-dose group, and 90% (45/50) of the high-dose group survived to the end of the 105-106 week study period. In females, 76% (38/50) of controls, 66% (33/50) of the low-dose group, and 56% (28/50) of the high-dose group survived to the end of the 105-106 week study period.

One low-dose male, 1 control female, and 1 high-dose female died during week 105 of natural causes.

CLINICAL SIGNS: No compound-related clinical signs observed.

BODY WEIGHT GAIN: Mean body weight gain of treated male mice comparable to control males. Mean body weight gain of female mice slightly higher than control females.

FEED/WATER CONSUMPTION: Average daily feed consumption per mouse by low- and high-dose mice was 97% of controls for males, and 97% and 103%, respectively, for females.

NEOPLASM FORMATION: A statistically significant positive trend (P<0.05) was observed in the incidence of histiocytic lymphomas in female mice. Combined incidence of lymphomas or leukemias (12%, 20%, 22%) was not statistically significantly elevated in treated female mice, relative to the controls.

A statistically significant positive trend (P<0.05) was observed in the incidence of liver adenomas or carcinomas in female mice (6% control, 8% low-dose, 16% high-dose). No statistically significant incidences of hepatocellular tumors occurred in male mice.

DISCUSSION: Authors report that tumors observed in treated mice were similar histopathologically to tumors observed in controls and to those typically observed in aging B6C3F1/N mice.

Although there was evidence for certain tumors observed (hepatocellular adenomas and carcinomas and histiocytic lymphomas in female mice), these incidences were within the historical ranges for female B6C3F1/N mice and therefore were not related to administration of the test substance. The authors and peer reviewers concluded that under the conditions of the study performed, stannous chloride was not carcinogenic for male or female B6C3F1/N mice.

Source : NTP. 1982
Test substance : Tin Dichloride [CAS No. 7772-99-8]; anhydrous, food grade ~98.5% purity, source: M&T Chemicals, Inc.
Reliability : (1) valid without restriction
Guideline study.

20.11.2003 (23)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : other: Wistar-derived
Route of admin. : gavage
Exposure period : days 6-15 of gestation
Frequency of treatm. : once/day x 10 days
Duration of test : 20 days
Doses : 0.5, 2.3, 11.0, and 50.0 mg/kg bw
Control group : yes, concurrent vehicle
Method : other: not reported
Year :
GLP : no
Test substance : other TS

Method : Virgin, adult, albino, female Wistar-derived rats were used for testing. Animals were housed individually, under controlled temperature and humidity. Food and water were provided ad libitum.

Female rats were mated and the presence of the vaginal sperm plug was designated as Day 0 of gestation. Females received the test substance by single gavage daily on Days 6 through 15 of gestation. Control animals received water only. A group of positive control animals received 250.0 mg/kg aspirin.

Body weights were recorded on days 0, 6, 11, 15, and 20 of gestation. Animals were observed daily for appearance, behavior, feed consumption, and body weight. On Day 20, pregnant animals were sacrificed and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. Body weights of live pups also were recorded. The urogential tract of each animal was examined. Gross examination was performed on all fetuses for the presence of external congenital abnormalities. 1/3 of the fetuses in each litter were examined for visceral abnormalities. The remaining 2/3 of the fetuses in each litter were examined for skeletal abnormalities.

Result : Total number of pregnancies to term on Day 20/total pregnancies, by dose administered:
0 mg/kg: 20/20
0.5 mg/kg: 22/23
2.3 mg/kg: 22/22
11.0 mg/kg: 23/23
50.0 mg/kg: 24/24
Positive control: 24/24

The average numbers of corpora lutea per pregnant dam were comparable between dose groups, ranging from 11.2 to 12.5.

Total number of live litters at 0, 0.5, 2.3, 11.0, 50.0 mg/kg and the positive control group were 20, 22, 22, 23, 24, and 19, respectively.
The average number of implantation sites per pregnant dam examined at term was 11.1, 11.3, 12.2, 12.3, 11.5, and 11.2 for the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups, respectively.

Total numbers of resorptions in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 8, 8, 5, 7, 5, and 94 respectively.

The total number of live fetuses in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 213, 249, 242, 275, 271, and 174, respectively.

Male/female sex ratios of live fetuses in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 0.84, 0.92, 0.95, 0.98, 1.13, and 0.78, respectively. There was 1 dead fetus in the positive control group and 3 dead fetuses in the 0.5 mg/kg dose group.

Average fetal body weights in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 3.53, 3.55, 3.67, 3.62, 3.72, and 2.29 g, respectively.

Skeletal findings, by dose group:
0 MG/KG: 15 fetuses in 11 litters had incomplete ossification of the sternebrae; 3 fetuses in 2 litters had wavy ribs; 13 fetuses in 8 litters had

incomplete closure of the skull; 7 fetuses in 6 litters were missing the hyoid; and 7 fetuses in 5 litters had reduced hyoid.

0.5 MG/KG: 30 fetuses in 15 litters had incomplete ossification of the sternebrae; 3 fetuses in 3 litters had missing sternebrae; 9 fetuses in 7 litters had wavy ribs; 31 fetuses in 11 litters had incomplete closure of the skull; 1 fetus in 1 litter had incomplete ossification of extremities; 16 fetuses in 9 litters were missing the hyoid; and 1 fetus in 1 litter had reduced hyoid.

2.3 MG/KG: 5 fetuses in 3 litters had incomplete ossification of the sternebrae; 1 fetus in 1 litter had missing sternebrae; 3 fetuses in 3 litters had wavy ribs; 1 fetus in 1 litter had incomplete ossification of vertebrae; 9 fetuses in 6 litters had incomplete closure of the skull; 8 fetuses in 5 litters were missing the hyoid; and 4 fetuses in 3 litters had reduced hyoid.

11.0 MG/KG: 11 fetuses in 6 litters had incomplete ossification of the sternebrae; 4 fetuses in 1 litter had missing sternebrae; 1 fetus in 1 litter had wavy ribs; 2 fetuses in 2 litters had incomplete ossification of vertebrae; 6 fetuses in 6 litters had incomplete closure of the skull; 11 fetuses in 6 litters were missing the hyoid; and 1 fetus in 1 litter had reduced hyoid.

50.0 MG/KG: 8 fetuses in 7 litters had incomplete ossification of the sternebrae; 1 fetus in 1 litter had missing sternebrae; 10 fetuses in 5 litters had wavy ribs; 19 fetuses in 10 litters had incomplete closure of the skull; 14 fetuses in 9 litters were missing the hyoid; and 3 fetuses in 3 litters had reduced hyoid.

POSITIVE (ASPIRIN) CONTROL: 99 fetuses in 18 litters had incomplete ossification of the sternebrae; 79 fetuses in 16 litters had missing sternebrae; 22 fetuses in 13 litters had incomplete ossification of ribs; 14 fetuses in 7 litters had fused/split ribs; 42 fetuses in 13 litters had wavy ribs; 7 fetuses in 5 litters had <12 ribs; 70 fetuses in 16 litters had >13 ribs; 106 fetuses in 18 litters had incomplete ossification of vertebrae; 7 fetuses in 4 litters had fused vertebrae; 16 fetuses in 7 litters had scoliosis; 83 fetuses in 18 litters had incomplete closure of the skull; 17 fetuses in 8 litters were missing the skull; 5 fetuses in 4 litters had incomplete ossification of extremeties; 73 fetuses in 18 litters were missing the hyoid; and 3 fetuses in 3 litters had reduced hyoid.

No soft tissue abnormalities were reported for the 0, 0.5, 2.3, 11.0, or 50.0 mg/kg dose groups. Soft tissue abnormalities reported for the positive (aspirin) control group included exencephaly, spina bifida, and. Enterohepatocele.

Average maternal body weights of surviving dams in all dose groups increased over the study period.

The authors concluded that "the administration of up to 50 mg/kg bw of the test material to pregnant rats for 10 consecutive days had no clearly discrenible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously" in the untreated control.

Source : Metal Carboxylates Coalition

Test substance : Tin Dichloride [CAS No. 7772-99-8]; white crystalline material, source and purity not reported.

Reliability : (2) valid with restrictions
Study predates GLP. Study lacks information on environmental conditions of housing, feed and water consumption, and characterization of test substance. Highest dose level did not induce overt maternal toxicity. No statistical analysis of data.

20.11.2003 (13)

Species	:	mouse
Sex	:	female
Strain	:	CD-1
Route of admin.	:	gavage
Exposure period	:	days 6-15 of gestation
Frequency of treatm.	:	once/day x 10 days
Duration of test	:	17 days
Doses	:	0.5, 2.3, 11.0, and 50.0 mg/kg bw
Control group	:	yes, concurrent vehicle
Method	:	other: not reported
Year	:	
GLP	:	no
Test substance	:	other TS

Method : Virgin, adult, albino, female CD-1 mice were used for testing. Animals were housed individually, under controlled temperature and humidity. Food and water were provided ad libitum.

Female mice were mated and the presence of the vaginal sperm plug was designated as Day 0 of gestation. Females received the test substance by single gavage daily on Days 6 through 15 of gestation. Control animals received water only. A group of positive control animals received 150.0 mg/kg aspirin.

Body weights were recorded on days 0, 6, 11, 15, and 17 of gestation. Animals were observed daily for appearance, behavior, feed consumption, and body weight. On Day 17, pregnant animals were sacrificed and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. Body weights of live pups also were recorded. The urogential tract of each animal was examined. Gross examination was performed on all fetuses for the presence of external congenital abnormalities. 1/3 of the fetuses in each litter were examined for visceral abnormalities. The remaining 2/3 of the fetuses in each litter were examined for skeletal abnormalities.

Result : Total number of pregnancies to term on Day 17/total pregnancies, by dose administered:
0 mg/kg: 21/21
0.5 mg/kg: 23/23
2.3 mg/kg: 23/23
11.0 mg/kg: 20/20
50.0 mg/kg: 21/21
Positive control: 20/20

The average numbers of corpora lutea per pregnant dam at 0, 0.5, 2.3, 11.0, 50.0 mg/kg and the positive control groups were 13.1, 14.4, 16.0, 14.4, 14.6, and 14.9, respectively.

Total number of live litters at 0, 0.5, 2.3, 11.0, 50.0 mg/kg and the positive control group were 21, 23, 23, 20, 21, and 19, respectively.

The average number of implantation sites per pregnant dam examined at term was 11.8, 12.1, 12.5, 12.3, 12.5, and 13.0 for the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups, respectively.

Total numbers of resorptions in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 18, 27, 15, 21, 14, and 16 respectively.

The total number of live fetuses in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 229, 249, 269, 223, 241, and 238, respectively.

Male/female sex ratios of live fetuses in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 1.08, 1.29, 1.13, 0.87, 0.96, and 1.93, respectively. There was 1 dead fetus in the negative control group, 4 dead fetuses in the 0.5 mg/kg group, 6 dead fetuses in the 2.3 mg/kg group, 2 dead fetuses in the 11.0 mg/kg group, 8 dead fetuses in the 50.0 mg/kg group, and 3 dead fetuses in the positive (aspirin) control group.

Average fetal body weights in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 0.91, 0.88, 0.90, 0.89, 0.86, and 0.80 g, respectively.

Skeletal findings, by dose group:
0 MG/KG: 67 fetuses in 19 litters had incomplete ossification of the sternebrae; 4 fetuses in 2 litters had bipartite sternebrae; 17 fetuses in 5 litters had missing sternebrae; 7 fetuses in 6 litters had >13 ribs; 1 fetus in 1 litter had incomplete ossification of vertebrae; 8 fetuses in 2 litters had incomplete ossification of extremities; 43 fetuses in 13 litters had missing hyoid; and 13 fetuses in 9 litters had reduced hyoid.

0.5 MG/KG: 105 fetuses in 21 litters had incomplete ossification of the sternebrae; 8 fetuses in 6 litters had bipartite sternebrae; 1 fetus in 1 litter had extra sternebrae; 26 fetuses in 10 litters had missing sternebrae; 11 fetuses in 8 litters had >13 ribs; 1 fetus in 1 litter had incomplete ossification of vertebrae; 2 fetuses in 2 litters had incomplete ossification of extremities; 26 fetuses in 11 litters had missing hyoid; and 21 fetuses in 13 litters had reduced hyoid.

2.3 MG/KG: 121 fetuses in 23 litters had incomplete ossification of the sternebrae; 10 fetuses in 8 littes had bipartite sternebrae; 22 fetuses in 7 litters had missing sternebrae; 13 fetuses in 8 litters had >13 ribs; 1 fetus in 1 litter had incomplete ossification of extremities; 29 fetuses in 14 litters had missing hyoid; and 22 fetuses in 12 litters had reduced hyoid.

11.0 MG/KG: 95 fetuses in 19 litters had incomplete ossification of the sternebrae; 6 fetuses in 5 litters had bipartite sternebrae; 13 fetuses in 7 litters had missing sternebrae; 11 fetuses in 7 litters had >13 ribs; 1 fetus in 1 litter had incomplete ossification of extremities; 29 fetuses in 14 litters had missing hyoid; and 22 fetuses in 13 litters had reduced hyoid.

50.0 MG/KG: 115 fetuses in 20 litters had incomplete ossification of the sternebrae; 7 fetuses in 5 litters had bipartite sternebrae; 34 fetuses in 12 litters had missing sternebrae; 8 fetuses in 5 litters had >13 ribs; 43 fetuses in 15 litters had missing hyoid; and 28 fetuses in 16 litters had reduced hyoid.

POSITIVE (ASPIRIN) CONTROL: 113 fetuses in 19 litters had incomplete ossification of the sternebrae; 7 fetuses in 7 litters had bipartite sternebrae;

37 fetuses in 16 litters had missing sternebrae; 8 fetuses in 7 litters had >13 ribs; 3 fetuses in 2 litters had incomplete ossification of extremities; 54 fetuses in 17 litters had missing hyoid; and 19 fetuses in 14 litters had reduced hyoid.

No soft tissue abnormalities were reported for the 0, 0.5, and 11.0 mg dose groups. In each of the 2.3 mg/kg, 50.0 mg/kg, and positive control groups, 1 fetus had meningoencephalocele.

Average maternal body weights of surviving dams in all dose groups increased over the study period.

The administration of up to 50 mg/kg bw of the test material to pregnant mice for 10 consecutive days had no clearly discrenible effect on nidation or on maternal or fetal survival.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; white crystalline material, source and purity not reported.
Reliability : (2) valid with restrictions
Study predates GLP. Study lacks information on environmental conditions of housing, feed and water consumption, and characterization of test substance. Highest dose level did not induce overt maternal toxicity. No statistical analysis of data.

20.11.2003 (13)

Species : rabbit
Sex : female
Strain : Dutch
Route of admin. : gavage
Exposure period : days 6-18 of gestation
Frequency of treatm. : once/day x 13 days
Duration of test : 28 days
Doses : 0.42, 1.90, 8.90, and 41.5 mg/kg bw/day
Control group : yes, concurrent vehicle
Method : other: not reported
Year :
GLP : no
Test substance : other TS

Method : Virgin, adult, female Dutch-belted rabbits were used for testing. Animals were housed individually, under controlled temperature and humidity. Food and water were provided ad libitum.

On day 0, each doe was injected with 0.4 ml of human chorionic gonadotropin in the marginal ear vein. Three hours post-injection, each doe was artificially inseminated with 0.3 ml of dilute semen. From day 6 through day 18 of gestation, groups of pregnant does (10-12 per treatment group) were intragastrically treated once per day with the test substance administered in water. Control rabbits received water only. A positive control group received 2.5 mg/kg of 6-aminonicotinamide on Day 9. Dose volume administered ranged from 1 to 6.4 ml/kg.

Body weights were recorded on days 0, 6, 12, 18, and 29 of gestation. Animals were observed daily for appearance, behavior, feed consumption, and body weight. On Day 29, pregnant animals were sacrificed and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. Body weights of live pups also were

recorded. The urogential tract of each animal was examined. Gross examination was performed on all fetuses for the presence of external congenital abnormalities. Live fetuses were incubated 24 hours to evaluate neonatal survival; surviving pups were sacrificed and examined for visceral abnormalities.

Result : Total number of pregnancies to term on Day 29/total pregnancies, by dose administered:
0 mg/kg: 10/10
0.42 mg/kg: 11/11
1.90 mg/kg: 11/12 (died or aborted before Day 29)
8.90 mg/kg: 10/11 (died or aborted before Day 29)
41.5 mg/kg: 10/11 (died or aborted before Day 29)
Positive control: 11/12 (died or aborted before Day 29)

The average numbers of corpora lutea per pregnant dam tended to increase with increasing dose level (from 8.36 at 0 mg/kg to 9.67 mg/kg at 41.5 mg/kg).

Total number of live litters was 10 at 0, 1.90, and 8.90 mg/kg; 11 at 0.42 mg/kg and the positive control; and 9 at 41.5 mg/kg.

The average number of implantation sites per pregnant dam examined at term was 4.30, 6.09, 4.91, 5.80, 5.40, and 6.27 for the 0, 0.42, 1.90, 8.90, 41.5 mg/kg and positive control groups, respectively.

Total numbers of resorptions in the 0.42, 1.90, 8.90, 41.5 mg/kg dose groups and the positive control group were 7, 5, 4, 7, and 8, respectively.

The total number of live fetuses 0, 0.42, 1.90, 8.90, 41.5 mg/kg dose groups and the positive control group were 43, 57, 49, 54, 47, and 61, respectively.

Male/female sex ratios of live fetuses in the 0, 0.42, 1.90, 8.90, 41.5 mg/kg dose groups and the positive control group were 1.26, 1.28, 1.45, 1.35, 1.24, and 0.97, respectively. There were 3 dead fetuses in the 0.42 mg/kg dose group.

Average fetal body weights in the 0, 0.42, 1.90, 8.90, 41.5 mg/kg dose groups and the positive control group were 39.9, 38.5, 37.9, 38.2, 42.3, and 32.5 g, respectively.

Skeletal findings, by dose group:
0 mg/kg: 2 fetuses in one litter had incomplete ossification of the sternebrae; 1 fetus in 1 litter had scrambled or bipartite sternebrae; and 1 fetus in 1 litter had acrania.

0.42 mg/kg: 1 fetus in 1 litter had incomplete ossification of the sternebrae; 2 fetuses in 2 litters had fused sternebrae; and 4 fetuses in 1 litter had extra sternebrae; and 2 fetuses in 1 litter had missing sternebrae.

1.90 mg/kg: No skeletal abnormalities reported.

8.90 mg/kg: 3 fetuses in 3 litters had incomplete ossification of the sternebrae; 2 fetuses in 2 litters had fused sternebrae; and 4 fetuses in 2 litters had extra sternebrae.

41.5 mg/kg: 2 fetuses in 2 litters had extra sternebrae and 1 fetus in 1 litter

had missing sternebrae.

Positive control group: 5 fetuses in 5 litters had incomplete ossification of the sternebrae; 2 fetuses in 2 litters had bipartite sternebrae; 5 fetuses in 3 litters had fused sternebrae; 1 fetus in 1 litter had extra sternebrae; 4 fetuses in 3 litters and fused or split ribs; 21 fetuses in 7 litters had scrambled vertebrae; 3 fetuses in 3 litters had scoliosis; 35 fetuses in 7 litters had tail defects; and 3 fetuses in 2 litters had incomplete closure of the skull.

Soft tissue abnormalities, by dose group:
0 mg/kg: 1 pup with cleft palate.

0.42 mg/kg: No abnormalities reported.

1.90 mg/kg: 1 pup had meningoencephalocele and 1 pup had medial rotation of hind limbs.

8.90 mg/kg: No abnormalities reported.

41.5 mg/kg: 1 pup had medial rotation of front limbs.

Positive control: Multiple abnormalities reported, including anopia, medial rotation of hind limbs, short tail, cleft palate, meningoencephalocele, and umbilical hernia.

Average maternal body weights of surviving dams in all dose groups increased over the study period.

The authors concluded that "the administration of up to 41.5 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discrenible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously" in the untreated control.

Source : Metal Carboxylates Coalition
Test substance : Tin Dichloride [CAS No. 7772-99-8]; white crystalline material, source and purity not reported.
Reliability : (2) valid with restrictions
Study predates GLP. Study lacks information on environmental conditions of housing, feed and water consumption, and characterization of test substance. Highest dose level did not induce overt maternal toxicity. No statistical analysis of data.

20.11.2003 (14)

Species : hamster
Sex : female
Strain : other: Golden
Route of admin. : gavage
Exposure period : days 6-10 of gestation
Frequency of treatm. : once/day x 5 days
Duration of test : 14 days
Doses : 0.5, 2.3, 11.0, and 50.0 mg/kg bw
Control group : yes, concurrent vehicle
Method : other: not reported
Year :
GLP : no

Test substance : other TS

Method : Virgin, adult, female golden hamsters were used for testing. Animals were housed individually, under controlled temperature and humidity. Food and water were provided ad libitum.

Female hamsters were mated and the presence of sperm in a vaginal smear was designated as Day 0 of gestation. Females received the test substance by single gavage daily on Days 6 through 10 of gestation. Control animals received water only. A group of positive control animals received 250.0 mg/kg aspirin.

Body weights were recorded on days 0, 8, 10, and 14 of gestation. Animals were observed daily for appearance, behavior, feed consumption, and body weight. On Day 14, pregnant animals were sacrificed and the numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were recorded. Body weights of live pups also were recorded. The urogential tract of each animal was examined. Gross examination was performed on all fetuses for the presence of external congenital abnormalities. 1/3 of the fetuses in each litter were examined for visceral abnormalities. The remaining 2/3 of the fetuses in each litter were examined for skeletal abnormalities.

Result : Total number of pregnancies to term on Day 14/total pregnancies, by dose administered:
0 mg/kg: 21/21
0.5 mg/kg: 21/21
2.3 mg/kg: 20/20
11.0 mg/kg: 21/21
50.0 mg/kg: 21/21
Positive control: 22/22

The average numbers of corpora lutea per pregnant dam at 0, 0.5, 2.3, 11.0, 50.0 mg/kg and the positive control groups were15.2, 15.1, 16.0, 16.4, 15.8, and 17.0, respectively.

Total number of live litters at 0, 0.5, 2.3, 11.0, 50.0 mg/kg and the positive control group were 20, 21, 19, 21, 21, and 22, respectively.

The average number of implantation sites per pregnant dam examined at term was 13.9, 12.4, 14.0, 14.1, 13.3, and 14.0 for the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups, respectively.

Total numbers of resorptions in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 21, 32, 19, 8, 15, and 31, respectively.

The total number of live fetuses in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 269, 249, 246, 286, 264, and 276, respectively.

Male/female sex ratios of live fetuses in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive control groups were 0.52, 0.53, 0.78, 0.73, 0.59, and 0.54, respectively. There was 1 dead fetus each in the negative control and positive control groups, 0 dead in the 0.5 mg/kg group, 13 dead in the 2.3 mg/kg group, 3 dead in the 11.0 mg/kg group, and 0 dead in the 50.0 mg/kg group.

Average fetal body weights in the 0, 0.5, 2.3, 11.0, 50.0 mg/kg and positive

control groups were 1.66, 1.67, 1.69, 1.67, 1.68, and 1.69 g, respectively.

Skeletal findings, by dose group:
0 MG/KG: 129 fetuses in 20 litters had incomplete ossification of the sternebrae; 28 fetuses in 16 litters had bipartite sternebrae; 2 fetuses in 1 litter had fused sternebrae; 43 fetuses in 13 litters had missing sternebrae; 15 fetuses in 12 litters had >13 ribs; 2 fetuses in 2 litters had incomplete ossification of vertebrae; and 1 fetus in 1 litter had missing hyoid.

0.5 MG/KG: 120 fetuses in 21 litters had incomplete ossification of the sternebrae; 22 fetuses in 14 litters had bipartite sternebrae; 28 fetuses in 12 litters had missing sternebrae; 43 fetuses in 17 litters had >13 ribs; 2 fetuses in 2 litters had incomplete ossification of extremities; and 1 fetus in 1 litter had reduced hyoid.

2.3 MG/KG: 101 fetuses in 17 litters had incomplete ossification of the sternebrae; 21 fetuses in 11 littes had bipartite sternebrae; 1 fetus in 1 litter had fused sternebrae; 18 fetuses in 9 litters had missing sternebrae; 40 fetuses in 18 litters had >13 ribs; 2 fetuses in 2 litters had missing hyoid; and 1 fetus in 1 litter had reduced hyoid.

11.0 MG/KG: 104 fetuses in 20 litters had incomplete ossification of the sternebrae; 28 fetuses in 15 litters had bipartite sternebrae; 37 fetuses in 12 litters had missing sternebrae; 38 fetuses in 17 litters had >13 ribs; and 1 fetus in 1 litter had missing hyoid.

50.0 MG/KG: 113 fetuses in 21 litters had incomplete ossification of the sternebrae; 20 fetuses in 11 litters had bipartite sternebrae; 1 fetus in 1 litter had extra sternebrae; 71 fetuses in 15 litters had missing sternebrae; 25 fetuses in 17 litters had >13 ribs; 1 fetus in 1 litter had incomplete ossification of vertebrae; 1 fetus in 1 litter had incomplete ossification of extremities; and 5 fetuses in 3 litters had missing hyoid.

POSITIVE (ASPIRIN) CONTROL: 144 fetuses in 22 litters had incomplete ossification of the sternebrae; 31 fetuses in 16 litters had bipartite sternebrae; 34 fetuses in 17 litters had missing sternebrae; 50 fetuses in 22 litters had >13 ribs; 1 fetus in 1 litter had scoliosis; 1 fetus in 1 litter had missing hyoid; and 1 fetus in 1 litter had reduced hyoid.

No soft tissue abnormalities were reported for the 0, 2.3, 11.0, 50 mg/kg, or positive control groups. In the 0.5 mg/kg dose group, 1 fetus had meningoencephalocele.

Average maternal body weights of surviving dams in all dose groups increased over the study period.

The authors reported that "administration of up to 50 mg/kg bw of the test material to pregnant hamsters for 5 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occuring spontaneously" in the untreated control group.

Source : Metal Carboxylates Coalition

Test substance : Tin Dichloride [CAS No. 7772-99-8]; white crystalline material, source and purity not reported.

Reliability : (2) valid with restrictions
Study predates GLP. Study lacks information on environmental conditions

of housing, feed and water consumption, and characterization of test substance. Highest dose level did not induce overt maternal toxicity. No statistical analysis of data.

20.11.2003 (13)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Tinplate has been used for over 100 years in food packaging, and worldwide usage is in the range of 80 billion cans per year. Dissolving of the tin into the canned foods or beverages will result in the presence of divalent tin in the products. The provisional Tolerable Weekly Intake for tin is 14 mg/kg and the recommended maximum permissible levels of tin in food are typically 200 – 250 mg/kg for solid foods and 150 mg/kg in beverages. In the last 25 years there have been no reports of acute effects atrributable to tin contamination in the range of 100 – 200 ppm, although slight gastrointesintal discomfort may occur in a small proprtion of those exposed. Adverse gastrointestinal effects have been reported in limited clinical studies at the level of 700 ppm and above. Studies using healthy adult volunteers demonstrated that levels up to 267 mg/kg tin in canned food cause no adverse effects and support the currently proposed tin levels of 200 mg/kg in canned beverages and 25O mg/kg in canned foods as safe for adults in the general population.

Computer modeling used to predict the chemical speciation of tin salts in tomato juice concluded that tin would not be absorbed after ingestion and that the observed toxic responses would be due to gastrointestinal irritation and not systemic poisoning.

(30)(31)

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT

201-15606B1

ROBUST SUMMARIES and SIDS DOSSIER for: 2-Ethylhexanoic Acid

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CAS No. 149-57-5

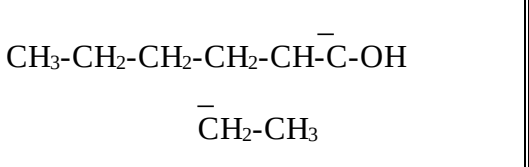
Sponsor Country: U.S.A.

DATE: Revised July 2001

CONTENTS

CONTENTS

SIDS PROFILE

1.1	CAS No.	149-57-5
1.2	CHEMICAL NAME	2-Ethylhexanoic acid
1.5	STRUCTURAL FORMULA	
	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	Acceptable	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.	N	-	-	-	-	-	N
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							

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
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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

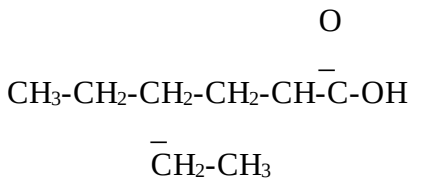
2.3 **Common Synonyms:**

á-Ethylcaproic acid
2-Ethylcaproic acid
á-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 **Physical-Chemical Data**

* 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. Eundam. 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. Eundam. 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. Eundam. 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.