FOREWORD INTRODUCTION

EPOXIDIZED OILS AND DERIVATIVES

CAS N°:

61789-01-3: Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP)
68609-92-7: 9-Octadecanoic acid (Z)-, epoxidized, ester W/propylene glycol (EODA)
8013-07-8: Epoxidized soybean oil (ESBO)
8016-11-3: Epoxidized linseed oil (ELSO or ELO)

SIDS Initial Assessment Report

For

SIAM 22

Paris, France, 18-21 April 2006

1. Category Name: Epoxidized Oils and Derivatives (EOD) Category

2. CAS Number and Chemical Name:

61789-01-3	Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP)
68609-92-7	9-Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (EODA)
8013-07-8	Epoxidized soybean oil (ESBO)
8016-11-3	Epoxidized linseed oil (ELSO or ELO)

3. Sponsor Country: United States

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4. Shared Partnership with: ICCA

American Chemistry Council Panel Manager
John Morris
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5. Roles/Responsibilities of the Partners:

- Name of industry sponsor /consortium: Epoxidized Oils and Derivatives Panel:

  Akcros Chemicals Ltd.
  Arkema Inc.
  Chemtura Corporation
  The Dow Chemical Company
  Ferro Corporation

- Process used: The EOD Panel produced the documents; EPA reviewed the documents and provided additional information where there were data gaps.

6. Sponsorship History

- How was the chemical or category brought into the OECD HPV Chemicals Programme?

Documents were prepared and reviewed by industry prior to submission to sponsor country. Sponsor country conducted reviews of submitted data and offered comments to industry. Industry prepared and resubmitted documents for consideration at SIAM 22.

no testing	(X)
testing	( )

7. Review Process Prior to the SIAM: The U.S. EPA reviewed, commented and edited this case.

8. Quality check process: Literature searches were conducted by the sponsor country to determine if all relevant data have been included in this submission.

9. Date of Submission: January 20, 2006

10. Comments: The four (4) epoxidized oils and derivatives form the Epoxidized Oils and Derivatives (EOD) Category based on structural and functional similarity.

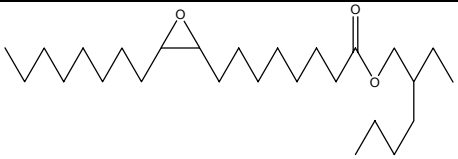
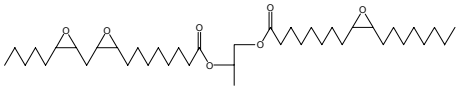
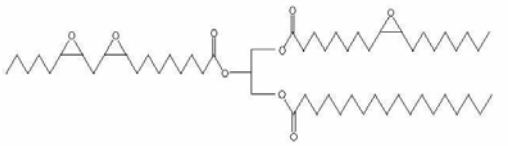
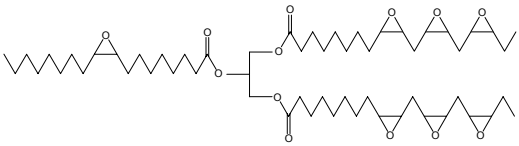
Acute toxicity data for 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO), are considered to be representative of 68609-92-7 (EODA).

Hydrolysis data for 61789-01-3 (ETP) is considered to be representative of 68609-92-7 (EODA), 8013-07-8 (ESBO) and 8016-11-3 (ELSO).

Biodegradation, genetic toxicity, repeated dose, reproductive and developmental data for 61789-01-3 (ETP) and 8013-07-8 (ESBO) are considered to be representative of 68609-92-7 (EODA) and 8016-11-3 (ELSO).

The aquatic effects discussion for 68609-92-7 (EODA) are considered to be representative of 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). The acute aquatic toxicity data for 8013-07-8 (ESBO) are considered to be representative of 61789-01-3 (ETP), 68609-92-7 (EODA) and 8016-11-3 (ELSO).

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	61789-01-3 Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP) 68609-92-7 9-Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (EODA) 8013-07-8 Epoxidized soybean oil (ESBO)
Chemical Name	Epoxidized Oils and Derivatives (EOD) Category
Structural Formula	 ETP  EODA  ESBO  ELSO

SUMMARY CONCLUSIONS OF THE SIAR

Category Justification

The four (4) epoxidized oils and derivatives form the Epoxidized Oils and Derivatives (EOD) Category based on structural and functional similarity. Epoxidized Oils and Derivatives are epoxidized fatty acid esters. The oils from which these products are derived are naturally occurring long chain fatty acid sources, and there is considerable overlap in the composition of the fatty acid portion of these products. They are primarily the C18 acids: oleic, linoleic, and linolenic acid. The alcohols are primary alcohols, diols or triols. This category consists of related fatty acid esters. Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP) 9-Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (EODA) Epoxidized soybean oil (ESBO) Epoxidized linseed oil (ELSO or ELO). ETP is a monoester with 2-ethylhexanol. EODA is a diester with propylene glycol. ESBO and ELSO are triesters with glycerol (triglycerides). These materials are considered a category for purposes of environmental and health hazard screening assessments because of their similarities in metabolism in microbial, aquatic and mammalian systems. Although there are no data regarding metabolism on these materials, it is known that fats are metabolized by esterases, and the materials in this category are fats. Carboxylesterases have been demonstrated to be present in many families of fish and aquatic invertebrates as well as mammals. The action of the esterase will result in a mixture of epoxidized fatty acids and 2-ethylhexanol from ETP, epoxidized fatty acids and propylene glycol from EODA, and epoxidized fatty acids and glycerol from ESBO and ELSO. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

Following metabolism, the alcohols from each material are a minor constituent of the metabolic products, and not produced in sufficient quantity to influence the toxicity profile of the EOD materials. The alcohols formed as metabolic products have already been assessed at previous SIAMs.

Acute toxicity data for 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO), are considered to be representative of 68609-92-7 (EODA). Hydrolysis data for 61789-01-3 (ETP) is considered to be representative of 68609-92-7 (EODA), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Biodegradation, genetic toxicity, repeated dose, reproductive and developmental data for 61789-01-3 (ETP) and 8013-07-8 (ESBO) are considered to be representative of 68609-92-7 (EODA) and 8016-11-3 (ELSO). The chronic daphnia data for 68609-92-7 (EODA) are considered to be representative of 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO).

Human Health

In mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides. Lipase is an enzyme that assists in the breakdown and digestion of fat in the body. Pancreatic lipase works at the oil/water interface since triglycerides are insoluble. During metabolism in the GI tract, pancreatic lipase preferentially hydrolyzes triglycerides to release the free fatty acids from the SN-1 and SN-3 (terminal) positions of the glycerol backbone. Other products of metabolism are mono- and diglycerides. The monoglycerides, diglycerides, and fatty acids can be absorbed. In a similar manner, pancreatic lipase and other digestive enzymes have been shown to hydrolyze propylene glycol monoesters and diesters in vitro. The absorption, metabolism and hydrolysis of propylene glycol distearate (which is structurally similar to EODA) were studied in rats using isotopically labelled compounds. These processes for the propylene glycol esters were found to be similar to those of the glycerol esters. So, there is evidence that the propylene glycol esters of fatty acids are hydrolyzed to propylene glycol and fatty acids. The ETP structure is similar to that of the monoglycerides, formed from the ELSO and ESBO. Further hydrolysis can also occur via carboxylesterase activity.

Numerous acute toxicity studies have been conducted with ETP, ESBO and ELSO via the dermal and oral route of exposure. Acute toxicity studies were not available for EODA. The dermal LD50s of ETP, ESBO and ELSO in rabbits range from greater than 16 mL/kg bw (ELSO) to greater than 20 mL/kg bw (ETP and ESBO). The oral LD50s of ETP, ESBO and ELSO in rats range from14.9 mL/kg bw (ELSO) to greater than 16 mL/kg bw (ETP) up to 41.5 mL/kg bw (ESBO). Similar acute toxicity values would be expected for EODA. There are no valid definitive skin irritation studies for any of the EOD materials, however the results from dermal toxicity studies with ETP, ESBO and ELSO indicate transient erythema and desquamation (no to slight skin irritation), similar effects are anticipated for EODA. Eye irritation studies are available for ETP and ESBO indicating no damage is observed, similar effects (no eye irritation) are expected for ELSO and EODA. Skin sensitization tests with ESBO and ETP indicate the EOD materials are not sensitizers.

Repeat dose studies by the oral route of exposure (gavage or dietary) have been conducted with ETP and ESBO. The NOAEL for ETP in a standard OECD Guideline 422 (rat) study was considered to be 1000 mg/kg bw/d (the highest dose tested). In a 90 day subchronic study, male and female rats were given 0.04, 0.2, 1.0 or 5.0% (5% is approximately 1.25 g/kg bw/d) ESBO. (Liver weights were increased in rats fed ESBO at 1% or 5% in diet. Gross findings indicated a test article-related effect of ESBO on liver and kidney at 1% and 5%. The NOAEL was 0.2% ESBO; the LOAEL was 1% ESBO. In a 2-year rat feeding study, a LOAEL of 1% ESBO was described based on increased liver and kidney weights. No effects were observed at .5% ESBO. Rats were given diets containing up to 5% ESBO for 15 weeks. Temporary slowed growth and liver and kidney enlargement at concentrations greater than 1.5% was observed. The LOAEL was greater than 1.5% ESBO. Groups of three dogs were fed up to 5% ESBO once per day for one year. Dogs fed 5% ESBO lost weight, and fatty liver changes (fatty infiltration) in one dog given 5% ESBO were observed. Food intake and body weight were decreased at 5% ESBO. The LOAEL was 5% ESBO. *In vitro*, ETP and ESBO were negative in bacterial or mammalian gene mutations assays. ETP and ESBO did not induce chromosomal aberrations in Chinese hamster V79 or human lymphocyte cells. EODA and ELSO are not expected to be mutagenic in bacterial or mammalian systems based on the lack of mutagenicity of ETP and ESBO.
Chronic/carcinogenicity studies were conducted with ESBO by the oral route (dietary). ESBO was not carcinogenic when fed to rats at up to 2.5% of the diet. Further, the NOAEL was 2.5% providing an average daily intake of approximately 1.0 g/kg bw in males and 1.4 g/kg bw in females. There were no treatment-related histopathologic lesions and there was no evidence of carcinogenicity of ESBO in groups of male and female rats given ESBO in the diet at 0, 0.1, 0.5, 1.0, 2.5, and 5.0%. A similar lack of carcinogenic response is expected for ETP, EODA and ELSO.

ETP and ESBO have been evaluated for the potential to cause developmental toxicity in rats and were not teratogenic, nor did they demonstrate reproductive toxicity. In a standard OECD Guideline 422 rat study with ETP, there were no adverse effects on reproductive parameters, and the NOAEL (maternal) and NOEL for reproduction was considered to

be 1000 mg/kg bw/d. Daily administration of ESBO up to 1000 mg/kg bw/d did not induce any toxic effect in parent male or female animals, did not disturb their capacity for reproduction and did not impair development of the F1 offspring. Based on the lack of reproductive toxicity or developmental effects with ETP and ESBO, EODA and ELSO are not expected to cause developmental toxicity or to demonstrate reproductive toxicity.

Environment

The melting point of the EOD materials range from <-23.2 to -2.2 C. All the EOD materials decompose at 176 – 204C; boiling points are not applicable. The vapor pressures of the EOD materials are less than 0.005 hPa. The reported vapor pressure values are presumed to reflect the the influence from minor impurities having relatively low boiling impurities. The estimated water solubilities of the EOD materials range from 0.937 to 6.65 mg/L. It is the nature of the EOD materials to form an emulsion upon mixing in water. They do not dissolve and they do not remain as individual molecules in solution, which reflects the difficulty with which the undissolved microemulsion is separated from true aqueous solution. The actual water solubility if the EOD substances are lower than reported. The log Kow values of these substances are estimated to be all greater than 6.2 according to the OECD Guideline No. 117: HPLC Method. Estimated half-lives for the indirect photolysis in the atmosphere range from (approximately) 2 to 5 hours for the four materials. Abiotic hydrolysis of these materials is slow in part due to the low water solubility of the materials; the hydrolysis half-life for ETP is greater than one year while the half-life of ESBO could not be determined. Level III Fugacity modeling, using loading rates for soil, and water of 1000 kg/h and 0 kg/h for air (due to the very low vapor pressure of these materials), shows the primary distribution to sediment (ranging from 65-69%) and soil (ranging from 27-32%). Biodegradation studies with ETP and ESBO indicate that these materials are readily biodegradable (70% within 28 days, OECD 301F test). ETP exhibited 70% degradation within 28 days in the OECD 301F test, whereas ESBO exhibited > 79% degradation over 28 days in the OECD 301B test. Previous studies showed lesser extents of biodegradation for these substances (21% of ETP, 0% of ESBO after 20 days). The discrepancy in results among these biodegradation studies can be attributed to differences in inoculum density, and more importantly, the degree to which the insoluble test substance is dispersed in the aqueous test mixtures. Based on data from ETP and ESBO, the EOD category is expected to be readily biodegradable. Whereas the estimated log Kow value of > 6.2 indicates a high potential for bioaccumulation of these substances, their uptake into fish is expected to be hindered by their large molecular size. If taken up by fish, these carboxylate ester-containing substances are expected to be readily metabolized and excreted. Thus, the bioaccumulation potential is expected to be much lower than predicted from log Kow alone.

Acute toxicity tests with fish (48 hr) as well as tests with both freshwater and marine crustacea (24 hr), and algae (72 hr) have been conducted with ESBO.. Although the fish and invertebrate studies were conducted for shorter time periods than currently specified in the OECD guidelines, for the time periods examined there was no or minimal evidence of toxicity observed at the limit of water solubility. In the algae study with ESBO, on the basis of biomass, the median effective concentration was 72 h EbC50 > 8 mg/L and 72 h NOEC = 2.3 mg/L. Effects are not expected to be observed below the water solubility of these materials. Based on the physicochemical properties of the category members (very low water solubility, log Kow values > 6.2, and readily biodegradable), as the substances are unlikely to be bioavailable to aquatic organisms. In preparation to conduct a chronic daphnia study it was demonstrated that there was no water soluble test substance detected above 0.05 mg EODA/L in a Water Accommodated Fraction (WAF) prepared from a loading of 100 mg/L. Therefore, considering the structure and low water solubility of EODA, it was concluded that the WAF is not likely to exert acute measurable effects on daphnids, and a chronic test would not be likely to provide meaningful, quantitative information on such effects. The option of conducting the chronic daphnia test with another member of the EOD family was considered. However, similar results are expected from the WAF preparations for these poorly soluble substances. Further laboratory investigation of the chronic toxicity of this substance to aquatic organisms is therefore deemed not necessary.

Exposure

The production volumes for the sponsor country in 2002 were:
ETP: up to 453 and less than or equal to 4536 tonnes
EODA: up to 453 and less than or equal to 4536 tonnes
ESBO: up to 45359 and less than or equal to 226,796 tonnes
ELSO: up to 453 and less than or equal to 4536 tonnes
ESBO and ELO are approved for use as inert ingredients in pesticides. EODA is a high monomeric epoxy plasticizer, which offers low volatility, low temperature flexibility and high compatibility in polyvinyl chloride systems. EODA is used in semi-rigid and flexible vinyl formulations, vinyl plastisol and organosols, coated fabrics and automotive interiors and moldings. ELSO and EODA are primarily used to keep plastics and rubber soft and pliable in flooring, upholstery, food packaging, hoses, tubing, blood bags and other products. The epoxy functionality provides excellent heat and light stability. ETP is used in flexible low temperature PVC application such as refrigerator gaskets.

These substances are used as plasticizers in PVC for a wide range of applications including food-contact materials where two of these materials have approvals under EU and FDA regulations. Migration does occur from plastics and in the case of ESBO for use in cap seals and use in PVC film a recent EFSA report has shown that the total adult intake is below the TDI, whilst in the case of baby jars the safety margins of the EU regulatory system have been eroded although the use is considered safe and industry is devising techniques to reduce the migration for baby food jars.

Additional dermal exposure may occur at low levels for consumers and this will be the main route of exposure for workers. In this case exposure may occur during filter cleaning operations, but these exposures are limited by appropriate protective clothing. Bulk storage, handling and transport of product further limit exposure potential by handling in enclosed storage vessels and piping. Automated container filling equipment is used to fill intermediate bulk containers, making exposure at this point in the process highly unlikely. Limited dermal exposure may occur with pesticide applicators where ESBO or ELO are used as inert ingredients. Inhalation exposure may occur during manufacture or processing, however these exposures are limited due to the low vapor pressures of these materials.

Some limited potential exists for release of material to the Publicly-Owned Treatment Works after primary biological treatment on site. Materials could potentially reach the primary treatment system as a result of inefficiencies in manufacturing processes. The chemical is stored in closed tanks and transported in tank cars and tank trucks, and smaller amounts are transported in drums or IBC's. Environmental release during transport is possible in the event of a spill or accident. The materials have very low vapor pressures, making airborne release unlikely.

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

The chemicals are currently of low priority for further work for human health and the environment because of their low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP) (CAS# 61789-01-3)
9-Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (EODA) (CAS# 68609-92-7)
Epoxidized soybean oil (ESBO) CAS# (8013-07-8)
Epoxidized linseed oil (ELSO or ELO) (CAS# 8016-11-3)

Epoxidized Oils and Derivatives are epoxidized fatty acid esters. The oils from which these products are derived are naturally occurring long chain fatty acid sources, and there is considerable overlap in the composition of the fatty acid portion of these products. They are primarily the C18 acids: oleic, linoleic, and linolenic acid. The alcohols are primary alcohols, diols or triols.

1.1 Identification of the Substance

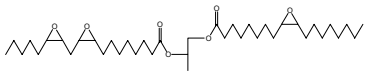
CAS Number: 61789-01-3 Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP)
68609-92-7 9-Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (EODA)
8013-07-8 Epoxidized soybean oil (ESBO)
8016-11-3 Epoxidized linseed oil (ELSO or ELO)

IUPAC Name: Not applicable

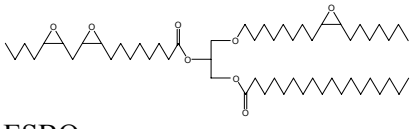
Molecular Formula: ETP: Unspecified (C26-H48-O4, per representative structure below)
EODA: Unspecified (C12H42O4, per representative structure below)ESBO: Unspecified (C57H101O8, per representative structure below)
ELSO: Unspecified (C57H95O13, per representative structure below)

Structural Formula:

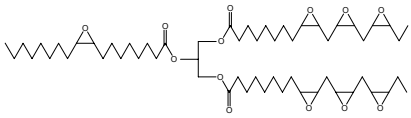
ETP



EODA



ESBO



ELSO

Molecular Weight: ETP: 424.74
EODA: 640
ESBO: 940-950
ELSO: 1037.39

Synonyms:

61789-01-3:
ETP
2-Ethylhexanol, tall oil fatty acids epoxidized ester
2-Ethylhexyl epoxytallates
Expoxidized 2-ethylhexyl ester of tall oil fatty acid
Fatty acid, tall oil, epoxidized, 2-ethylhexyl ester
Fatty acids, tall oil, epoxidized, 2-ethylhexyl esters
Fatty acids, tall-oil, 2-ethylhexyl esters, epoxidized
Flexol EP-8 (separate here)
sec-Octyl epoxytallate

68609-92-7:
EODA
9-Octadecenoic acid (Z)-, epoxidized, ester with propylene glycol
Oleic acid, 1,2-propylene glycol epoxidized ester

8013-07-8:
ESBO
Admex E LO
Drapex 6.8
Epocizer P 206
Epoxidized soy oils
Epoxidized soya oils
Epoxizer P 206
Epoxol EPO
Fatty acid, soybean oil, epoxidized
Fatty acid, soybean oil, epoxidized: flexol epo
Flexol EPO
G-62
Kronox S
P 206 (VAN)
PX-800
Reoplast 39
Soyabean oil, epoxidized
Plas-Chek 775

8016-11-3:
ELSO
ELO
Adekacizer O 180
Drapex 10.4
Epoxidized linseed oil
Epoxidized linseed oils
Epoxol 9-5
Linseed oil, epoxidized

ETP is derived from long chain saturated and unsaturated fatty acids and 2-ethylhexanol:

C_8H_{17} - OR
[Where R = fatty acid side chain, unsaturated or saturated of varying carbon length (95% is C_{18})]. Tall oil fatty acid is derived from pine trees. Tall oil fatty acid is a mixture of fatty acids, with a typical fatty acid distribution of stearic (2.2%), oleic (58.6%), and linoleic (36%) acids constituting

the major unsaturated fatty acid components. Saturated fatty acid components constitute about 2.2% of the mixture. It may also contain some rosin acids. Epoxidation at most or all of the points of unsaturation in the fatty acid chains gives a variety of products collectively known as fatty acids, tall-oil epoxidized, 2-ethylhexyl esters. The alcohol portion of this molecule is 2-ethylhexanol.
There are a number of similar products on the market that are similar to ETP as defined. These products are based on fatty acids sourced from other naturally occurring fatty acids with a composition that can be described by:

- C_{16-18} and C_{16} unsaturated fatty acids
- Rape oil Fatty acids
- Rape oil, low euricic acid, fatty acids
- C_{14-22} and C_{16-22} unsaturated fatty acids.

EODA is derived from fatty acids esterified with propylene glycol:

CH_3 - CHOR - CH_2OR
[Where R = fatty acid side chain, unsaturated or saturated of varying carbon length (95% is C_{18})].
EODA is derived primarily from oleic acid. EODA is a diester with a typical fatty acid distribution of linoleic acid (8%), oleic acid (73%), linolenic acid (1%), myristoleic acid (3%), myristic acid (3%), palmitic acid (4%), palmitoleic acid (7%), and traces of stearic and lauric acids. Saturated fatty acid components constitute about 7% of the mixture. Epoxidation at most or all of the points of unsaturation in the fatty acid chains gives a variety of products collectively known as EODA.

ESBO and ELSO are triglycerides of the general structure:

CH_2OR - CHOR - CH_2OR
[Where R = fatty acid side chain, unsaturated or saturated of varying carbon length (95% is C_{18})].
Soybean oil, the natural product from which ESBO is derived, is a triglyceride, with a typical fatty acid distribution of linoleic (49-57%), oleic (26-36%), and linolenic (1-2%) acids constituting the major unsaturated fatty acid components. Saturated fatty acid components constitute about 14% of the mixture. Epoxidation at most or all of the points of unsaturation (double bonds between carbon atoms) in the fatty acid chains gives a variety of products collectively known as epoxidized soy bean oil. The alcohol portion of this molecule is glycerol. Epoxidized linseed oil is derived from the natural product, linseed or flaxseed. Linseed oil is a triglyceride, with a typical fatty acid distribution of palmitic (5.5%), stearic (3.5%), oleic (19.1%), linoleic (15.3%), and linolenic (56.6%) acids constituting the major unsaturated fatty acid components. Saturated fatty acid components constitute about 9% of the mixture. Expoxidation at most or all of the points of unsaturation in the fatty acid chains gives a variety of products collectively known as epoxidized linseed oil. The alcohol portion of this molecule is glycerol.

The structural differences between the four materials in this category reflect differences in the degree of epoxidation and their alcohol functionality.

1.1.2 Category Justification

As described above, this category consists of related fatty acid esters. ETP is a monoester with 2-ethylhexanol. EODA is a diester with propylene glycol. ESBO and ELSO are triesters with glycerol (triglycerides). These materials are considered a category for purposes of environmental

and health hazard screening assessments because of the similarities metabolism (uptake results in rapid metabolism by esterases) of these materials in microbial, aquatic and mammalian systems. Carboxylesterases have been demonstrated to be present in many families of fish and aquatic invertebrates as well as mammals (Miller et al., 1981, Sugihara et al., 1994, Escartin and Porte, 1997 and Barron et al., 1999). The action of the esterase will result in a mixture of epoxidized fatty acids and 2-ethylhexanol from ETP, epoxidized fatty acids and propylene glycol from EODA, and epoxidized fatty acids and glycerol from ESBO and ELSO. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

While there is no specific information on the metabolism of these materials, there is a large body of research on the metabolism and absorption of vegetable oils. Because of the similarity in physicochemical properties of these materials, it is assumed that they are absorbed and metabolized in a manner similar to vegetable oils, rather than simply excreted. This assumption is supported by the liver effects in the 28 day feeding study of ETP (lowest MW material) and the chronic feeding studies with ESBO (higher end of MW range), indicating a response to absorbed materials. The backbone molecules of these esters have all been through SIAM; ethylhexanol (2-EH) SIAM 3, propylene glycol (PG) SIAM 11 and glycerol (GLY) SIAM14. The tall oil fatty acid side chains remain the primary metabolic products and the backbone amounts are estimated to be: 2-EHA is ~30%; the PG is ~12% and the GLY ~ 9 - 10%.

In mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides.

The ETP structure is similar to that of the monoglycerides, formed from the ELSO and ESBO. Further hydrolysis can also occur via carboxylesterase activity.

Acute toxicity data for 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO), are considered to be representative of 68609-92-7 (EODA). Hydrolysis data for 61789-01-3 (ETP) is considered to be representative of 68609-92-7 (EODA), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Biodegradation, genetic toxicity, repeated dose, reproductive and developmental data for 61789-01-3 (ETP) and 8013-07-8 (ESBO) are considered to be representative of 68609-92-7 (EODA) and 8016-11-3 (ELSO). The chronic daphnia data for 68609-92-7 (EODA) are considered to be representative of 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). These data are described in more detail in the relevant sections below.

1.2 Purity/Impurities/Additives

The four substances do not have any additives or solvents, and are described above. Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Name: Value	Reference
Physical state	All are liquids	
Melting point (^{o}C)	ETP: <-23.2 (measured) EODA: -4.2 (measured) ESBO: -2.2 (measured) ELSO: -2.2 (measured)	Safepharm Laboratories, 2002a Safepharm Laboratories, 2002b Safepharm Laboratories, 2002c Safepharm Laboratories, 2002d
Boiling point (^{o}C)	All decompose at 176-204	Safepharm Laboratories, 2002a ,b, c, d
Relative density	ETP: 0.92 g/cm^3 at 25 ^{o}C (measured, but of limited reliability) EODA: 0.9490-0.9551 g/cm^3 at 25 ^{o}C (measured) ESBO: 0.9875-0.9930 g/cm^3 at 25 ^{o}C (measured) 0.994-0.998 g/cm^3 at 25 ^{o}C ELSO: 1.03 g/cm^3 at 20 ^{o}C (measured but of limited reliability)	Crompton Corporation, 2005 Arkema, 2005 Arkema, 2005 Weil, CS et al., 1963 Dow Chemical, 2005
Vapour pressure (Pa at 25^{o}C) (1)	ETP: <.001 (estimated) EODA: =.005 (estimated) ESBO: =<.001 (estimated) ELSO: =<.001 (estimated)	Safepharm Laboratories, 2002e, f, g, h
Water solubility (g/L at 20^{o}C) (2)	ETP: =.00297 (estimated) EODA: =.00665 (estimated) ESBO: =.00099 (estimated) ELSO: =.000937 (estimated)	Safepharm Laboratories, 2002a Safepharm Laboratories, 2002b Safepharm Laboratories, 2002c Safepharm Laboratories, 2002d
Partition coefficient n-octanol/water (log value)(3)	All > 6.2 (estimated)	Safepharm Laboratories, 2002a, b, c, d
Henry's law constant	Not available	
Saturated fatty acid components (%)	ETP: 2.2 EODA: 7 ESBO: 14 ELSO: 9	EOD Panel, 2003
Epoxy values (%)(4)	ETP: 4.5-4.7 EODA: 4.6-4.8 ESBO: 6.8-7.1 ELSO: 9-10	EOD Panel, 2003

(1) The vapor pressure of the EOD materials is below the ability to measure, which is expected based on the high molecular weights of these materials. The reported vapor pressure values are presumed to reflect the influence from minor impurities having relatively low boiling points.

(2) It is the nature of these EOD materials to form an emulsion upon mixing in water. They do not dissolve and they do not remain as individual molecules in solution, which reflects the difficulty with which the undissolved microemulsion is separated from true aqueous solution. This was confirmed in the attempts to prepare appropriate water accommodated fractions (WAF) of EODA (CAS number 68609-92-7), which did not contain

dissolved test substance at or above the method detection limit of 0.05 mg/L. These results from the WAF preparation suggest that actual water solubility of the EOD substances are lower than reported above.

(3) OECD 117 HPLC Method ; values eluted after DDT standard

(4) The "epoxy value" indicates the percentage of total test substance mass which is attributed to epoxy functional group. The epoxy value thus indicates the degree of epoxidation of the test substance, which is important for determining compliance with their use in food-contact applications.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The production volumes for the sponsor country in 2002 were:

ETP: between 453 and 4536 tonnes
EODA: between 453 and 4536 tonnes
ESBO: between 45359 and 226,796 tonnes
ELSO: between 453 and 4536 tonnes

ESBO and ELSO are approved for use as inert ingredients in pesticides; the product is used as an acid scavenger to protect the application equipment from corrosion rather than as an active ingredient in the pesticide. (USEPA, 2004). EODA is a high monomeric epoxy plasticizer which offers low volatility, low temperature flexibility and high compatibility in polyvinyl chloride systems. EODA is used in semi-rigid and flexible vinyl formulations, vinyl plastisol and organosols, coated fabrics and automotive interiors and moldings (Arkema, 2005). ELSO and EODA are primarily used to keep plastics and rubber soft and pliable in flooring, upholstery, food packaging, hoses, tubing, blood bags and other products (Arkema, 2005). The epoxy functionality provides excellent heat and light stability. ETP is used in flexible low temperature PVC application such as refrigerator gaskets (Arkema, 2005).

These substances are used as plasticizers in PVC for a wide range of applications including food-contact materials where two of these materials have approvals under EU and FDA regulations. Migration does occur from plastics and in the case of ESBO for use in cap seals and use in PVC film a recent EFSA report has shown that the total adult intake is below the TDI, whilst in the case of baby jars the safety margins of the EU regulatory system have been eroded although the use is considered safe and industry is devising techniques to reduce the migration for baby food jars.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

In production, these materials are handled in closed systems. Necessary engineering controls during production include proper ventilation, containment, safety equipment and actual hardware designed to minimize exposure, through splashing, or exposure to the air. Transfer of these materials is in closed pipe systems rather than in open systems to minimize loss. There may be low levels losses in process waters, which are discharged to a waste water treatment system. Some limited potential exists for release of material to the POTW after primary biological treatment on site. Materials could potentially reach the primary treatment system as a result of inefficiencies in manufacturing processes. The chemical is stored in closed tanks and transported in tank cars and tank trucks, and smaller amounts are transported in drums or Intermediate Bulk Containers (IBCs). Environmental

release during transport is possible in the event of a spill or accident. The materials have very low vapor pressures, making airborne release very unlikely.

These substances are used as plasticizers in PVC for a wide range of applications including food-contact materials where two of these materials have approvals under EU and FDA regulations. Migration does occur from plastics and in the case of ESBO for use in cap seals and use in PVC film a recent EFSA report has shown that the total adult intake is below the TDI, whilst in the case of baby jars the safety margins of the EU regulatory system have been eroded although the use is considered safe and industry is devising techniques to reduce the migration for baby food jars.

2.2.2 Photodegradation

Photodegradation half-lives for the four materials range from (approximately) 2 to 5 hours (AopWin v1.90, 2002).

Table 2 Summary of photodegradation modeling

	ETP	**EODA**	**ESBO**	**ELSO**
Half-life (hours)	4.2	3	1.9	2.2
Rate constant (cm^3/(molecule*sec)	30.2514 E-12	42.4033 E-12	66.4071 E-12	57.9673 E-12

2.2.3 Stability in Water

Abiotic hydrolysis of these materials is slow in part due to the low water solubility of the materials; the hydrolysis half-life for ETP is greater than one year (Safepharm Laboratories, 2002a). The hydrolysis half-life of ESBO could not be determined due to the negligible solubility of the test material in water, 1.36 x 10-3 g/L of solution at 20.0 +/- 0.5 deg C. Secondly and more critically, the ESBO found in solution during the water solubility study represented only the lower molecular weight range of the test material components. Therefore working at half this water solubility value, the maximum concentration permitted by the method guideline, was not applicable since the value does not address the more abundant, higher molecular weight fraction of ESBO. (Safepharm Laboratories, 2002c). In general, these materials are expected to hydrolyze very slowly.

Table 3 Summary of hydrolysis studies

Half-life				
pH at 25C	**ETP**	**EODA**	**ESBO**	**ELSO**
4	> 1 year	Not determined*	Not relevant; see text *	Not determined*
7	> 1 year	Not determined*	Not relevant; see text *	Not determined*
9	> 1 year	Not determined*	Not relevant; see text *	Not determined*

* = Hydrolysis half-life not determined. Read across to ETP.

2.2.4 Transport between Environmental Compartments

Level III Fugacity modeling, using loading rates for soil and water of 1000 kg/h, with air set at 0 kg/hr (due to the very low vapor pressure of these materials), shows the following percent distribution(EPIWIN v3.05, 2002):

Table 4 Summary of level III fugacity modeling

	ETP	EODA	ESBO	ELSO
Air	8.02e-006	4.41e-014	6.45e-022	5.14e-026
Water	7.3	3.49	3.49	1.28
Soil	27.9	27.2	27.2	31.6
Sediment	64.8	69.4	69.4	67.1

2.2.5 Biodegradation

Biodegradation studies with ETP (Bloss, T.B., 1996 and RCC, 2005a) indicate that this material is biodegradable (70%) within 28 days (OECD 301F), but does not meet the criteria of "readily biodegradable" because it did not meet the 10 day criterion window. A forthcoming revision to the OECD Guidelines for Testing Chemicals indicates that the 10 day window should not be applied to interpretation of ready biodegradability test results for mixtures of structurally similar chemicals, such as oils and surfactants (OECD Draft revised Introduction to Section 3 of the OECD Test Guidelines: Biodegradation and Bioaccumulation, July 2003 version). In tests of such substances, a sequential biodegradation of the individual components is anticipated, leading to inaccurate quantitation of the degradation rate for individual structures (Richterich and Steber, 2001). Therefore, the 10-day window is not applied in assessing the ready biodegradability of this test substance. In a second study, 21% degradation of ETP occurred after 20 days, which is not considered readily biodegradable. The difference in results between the two biodegradation studies is due to a difference in study design between the two studies. Silica gel was used to increase surface area of ETP in the OECD 301F test, resulting in 70% degradation in 28 days. ESBO was found to be "readily biodegradable" (79% after 28 days; OECD 301B) in a standard CO2 evolution test (CIBA-GEIGY Ltd., 1988a). In a second study, ESBO was not readily biodegradable under test conditions that are similar to those in the OECD 301 series (Price, 1974b), using acclimated sludge. No biodegradation was observed when non-acclimated sludge was used. The main uncertainty in this second study resides in the concentration of the inoculum, which was not explicitly determined. The difference in results between the biodegradation studies with ESBO is due to a difference in study design between the studies.

The differences in the results observed in the above biodegradation studies can be summarized as follows: The category substances are poorly soluble in water, and undissolved substance is observed to float on the water surface. In the absence of their mixing or dispersion in aqueous test media, minimal contact with the microbial inoculum is expected in a biodegradation test. The OECD 301B and 301F tests employ continuous stirring of the aqueous test mixture under a headspace, as well as a relatively high inoculum density (30 mg/L susp. solids). These OECD test guidelines were used to demonstrate the ready biodegradability of ESBO and ETP. Previously, the closed-bottle test procedure described by APHA was used to evaluate biodegradability of these same substances, and showed significantly reduced extents of degradation. The APHA closed-bottle procedure employs a static incubation of the biodegradation test mixtures in liquid-full

bottles. The closed-bottle procedure also employs a very dilute inoculum. It is therefore not surprising that the closed bottle tests showed poor biodegradation of the ESBO and ETP substances, whereas ready biodegradability was observed with the OECD 301F and 301B tests. Based on data from ETP and ESBO, the EOD category is expected to be readily biodegradable.

Table 5 Summary of biodegradation studies

Test Substance	Test Guideline	RESULT	COMMENT	Reference
ETP	OECD 301F Am Public Health Assoc., 1989 and Price, et al., 1974a	70% after 28 days 21% after 20 days	Biodegradable Not readily Biodegradable	RCC, 2005a Bloss, T.B., 1996
EODA	No data	-	Expected to be biodegradable; read across to both ETP and ESBO	RCC, 2005a Bloss, T.B., 1996 CIBA GEIGY Ltd., 1988a Price, 1974b
ESBO	OECD 301B Similar to OECD 301	79% after 28 days 24% after 20 days (acclimated sludge) 0% after 20 days (non-acclimated sludge)	Readily biodegradable Not readily Biodegradable No biodegradation	CIBA GEIGY Ltd., 1988a Price, 1974b
ELSO	No data	-	Expected to be biodegradable; read across to both ETP and ESBO	RCC, 2005a Bloss, T.B., 1996 CIBA GEIGY Ltd., 1988a Price, 1974b

2.2.6 Bioaccumulation

The potential for bioaccumulation of the EOD materials was calculated using EPIWIN (V3.11). Based on the EOD materials having high partition coefficient values (greater than 6.2 (Safepharm, 2002a, b, c, d)) and modelling results (Table 6), the bioconcentration is likely to be low for all four materials (BCF = 375).

Table 6 Summary of calculated bioconcentration factors

	ETP	EODA	ESBO	ELSO
Log Kow	>6.2	>6.2	>6.2	>6.2
Estimated BCF *	375	375	375	375

* = Estimated using EPIWIN(v3.11)

2.3 Human Exposure

2.3.1 Occupational Exposure

The most likely route of human exposure to these materials is via dermal contact. Exposure may occur during manufacture or processing, however these exposures are limited due to the low vapor pressures of the materials. Exposure may occur during filter cleaning operations, but these exposures are limited by appropriate protective clothing. Bulk storage, handling and transport of product further limit exposure potential by handling in enclosed storage vessels and piping. Automated container filling equipment is used to fill drums and IBC's, thus making exposure during this process highly unlikely. Limited dermal exposure may occur with pesticide applicators where ESBO or ELO are used as inert ingredient.

2.3.2 Consumer Exposure

These substances are used as plasticizers in PVC for a wide range of applications including food-contact materials where two of these materials have approvals under EU and FDA regulations. Migration does occur from plastics and in the case of ESBO for use in cap seals and use in PVC film a recent EFSA report has shown that the total adult intake is below the TDI, whilst in the case of baby jars the safety margins of the EU regulatory system have been eroded although the use is considered safe and industry is devising techniques to reduce the migration for baby food jars.

Additional dermal exposure may occur at low levels for consumers and this will be the main route of exposure for workers. In this case exposure may occur during filter cleaning operations, but these exposures are limited by appropriate protective clothing. Bulk storage, handling and transport of product further limit exposure potential by handling in enclosed storage vessels and piping. Automated container filling equipment is used to fill intermediate bulk containers (IBCs), making exposure at this point in the process highly unlikely. Limited dermal exposure may occur with pesticide applicators where ESBO or ELO are used as inert ingredients. Inhalation exposure may occur during manufacture or processing, however these exposures are limited due to the low vapor pressures of these materials.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

As described in 1.1.2 this category consists of related fatty acid esters. ETP is a monoester with 2-ethylhexanol. EODA is a diester with propylene glycol. ESBO and ELSO are triesters with

glycerol (triglycerides). These materials are considered a category for purposes of health hazard screening assessments because of the similarities of routes of uptake and metabolism of these materials in mammalian systems. Because the metabolic products are similar as and the data for the products, which have been tested, indicate consistent responses, this group of products can be evaluated as a category for a health assessment screening.

Lipase is an enzyme that assists in the breakdown and digestion of fat in the body. Pancreatic lipase works at the oil/water interface since triglycerides are insoluble. During metabolism in the GI tract, pancreatic lipase preferentially hydrolyzes triglycerides to release the free fatty acids from the SN-1 and SN-3 (terminal) positions of the glycerol backbone. Other products of metabolism are mono- and diglycerides. The monoglycerides, diglycerides, and fatty acids can be absorbed (World Health Organization, 1974)

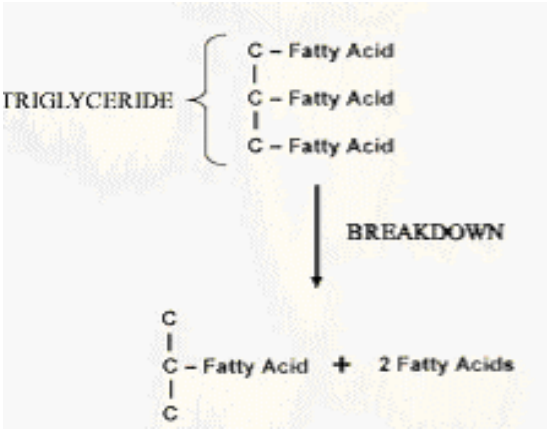


Diagram excerpted from: Enova™ Brand Food Oil: Functional Fat from Japan Goes Stateside Ralph Ofcarcik, Ph.D.Director of Nutrition Services, http://www.redmountainspa.com/_health_ education_fitness/articles/enova.html

In a similar manner, pancreatic lipase and other digestive enzymes have been shown to hydrolyze propylene glycol monoesters and diesters in vitro. The absorption, metabolism and hydrolysis of propylene glycol distearate (which is structurally similar to EODA) were studied in rats using isotopically labelled compounds. These processes for the propylene glycol esters were found to be similar to those of the glycerol esters. So, there is evidence that the propylene glycol esters of fatty acids are hydrolyzed to propylene glycol and fatty acids. (World Health Organization, 1967).

3.1.2 Acute Toxicity

Numerous acute toxicity studies have been conducted with ETP, ESBO and ELSO via the dermal and oral route of exposure. Acute toxicity studies were not available for EODA.

Studies in Animals

Dermal

The dermal LD50s of ETP, ESBO and ELSO in rabbits indicate a low order of toxicity. Similar toxicity values are expected for EODA. ETP was applied to the skin of three rabbits for 24 hours at a dose of 20 mL/kg bw (Carpenter, C.P., 1959). One rabbit had desquamation but the other two had no skin reactions. The dermal LD50 was >20 mL/kg bw. A dosage of 20 mL/kg bw of ESBO resulted in survival of all four rabbits (Mellon Institute of Research, 1955, BIBRA, 1988, BIBRA, 1997, and Weil, CS et al., 1963). No particular damage other than transient erythema resulted. ELSO was applied to the skin of 7 rabbits for 24 hours at a dose of 16 mL/kg bw (Carnegie-Mellon

Institute of Research, 1977). The animals showed signs of erythema. Diarrhea was observed at the time of death in the one animal that died, and at necropsy the kidneys were pale. In survivors, there were no reported signs of toxicity and at necropsy the kidneys were mottled. The LD50 was greater than 16 mL/kg bw.

Table 7 Summary of acute dermal toxicity (rabbits)

Test Substance	Reported LD50	Reference
ETP	>20 mL/kg bw	Carpenter, C.P., 1959
ESBO	>20 mL/kg bw	Mellon Institute of Research, 1955, BIBRA, 1988, BIBRA, 1997, and Weil, CS et al., 1963
ELSO	>16 mL/kg bw	Carnegie-Mellon Institute of Research, 1977
EODA	No data*	

* = A similar order of acute toxicity is expected for EODA as observed for ETP, ESBO and ELSO.

Oral

Groups of 5 male albino rats were dosed with ETP by gavage at 8, 16, 32 or 64 mL/kg bw and followed for 14 days (Carpenter, C.P., 1959). All animals dosed with 8 or 16 mL/kg bw survived the entire 14 day period. All animals dosed with 32 mL/kg bw died 1-3 days after dosing. At the highest dose level, all rats died 1-2 days after dosing. Rats that died at 32 and 64 ml/kg had congested lungs, mottled or pale livers, pale kidney surfaces with congested interiors and slightly congested adrenals. The LD50 of ETP was greater than 16 mL/kg bw. The LD50 (gavage) of ESBO in a group of ten rats was greater than 5000 mg/kg bw (CIBA-GEIGY Ltd., 1981). Groups of five rats were dosed with ESBO by gavage at doses of 7.95, 15.8, 31.6 or 63 mL/kg bw (high dose consisted of 4 rats) (Mellon Institute of Research, 1955, BIBRA, 1988, BIBRA, 1997, and Weil, CS et al., 1963). Lethality was observed at 15.8, 31.6 and 63.0 mL/kg bw. There were no marked symptoms of distress noted in animals dosed with 63.0 mL/kg bw. At 31.6 and 15.8 mL/kg bw, the rats that died had congested lungs, mottled livers, pale kidneys with congested interiors and considerable intestinal irritation. The LD50 was reported to be 22.5 mL/kg bw. Rats were dosed by gavage with five levels of ESBO (differing by a factor of two in a geometric series) and the LD50 calculated after a 14 day observation period (Carnegie-Mellon Institute of Research, 1976). The LD50 was reported to be 41.5 mL/kg bw. ELSO was administered to groups of five rats by gavage at dosage levels 4, 8, 16 and 32 mL/kg bw (Carnegie-Mellon Institute of Research, 1977). There were no deaths at 4 and 8 mL/kg bw, three animals died at 16 mL/kg bw, and all animals died at 32 mL/kg bw. Gross pathology observations were noted in the lung, liver, spleen, kidney, adrenals, stomach and intestines of animals that died. In survivors, gross pathology observations included the lungs, livers, kidneys, intestines and adrenals. A similar order of acute toxicity is expected for EODA as observed for ETP, ESBO and ELSO.

Table 8 Summary of acute oral toxicity (rats)

Test substance	Reported LD50	Reference
ETP	>16 mL/kg bw	Carpenter, C.P., 1959
ESBO	>5000 mg/kg bw	CIBA-GEIGY Ltd., 1981
	22.5 mL/kg bw	Mellon Institute of Research, 1955, BIBRA, 1988, BIBRA, 1997, and Weil, CS et al., 1963
	41.5 mL/kg bw	Carnegie-Mellon Institute of Research, 1976

Test Substance	Reported LD50	Reference
ELSO	14.9 mL/kg bw	Carnegie-Mellon Institute of Research, 1977
EODA	No data*	

* = A similar order of acute toxicity is expected for EODA as observed for ETP, ESBO and ELSO.

Studies in Humans

No data available.

3.1.3 Irritation

Studies in Animals

There are no valid skin irritation studies for any of the EOD materials. However, test conducted under the more severe conditions of dermal toxicity studies (20 mL/kg bw applied for a 24-hour contact period) provide valuable information regarding the dermal irritation potential of the EOD materials. When ETP was applied to the skin of three rabbits for 24 hours at a dose of 20 mL/kg bw (Carpenter, C.P., 1959), one rabbit had desquamation but the other two had no skin reactions. When ESBO was applied to the skin of four rabbits for 24 hours at a dose of 20 mL/kg bw (Mellon Institute of Research, 1955; BIBRA, 1988, 1997; and Weil, CS et al., 1963), only transient erythema resulted. When ELSO was applied to the skin of 7 rabbits for 24 hours at a dose of 16 mL/kg bw (Carnegie-Mellon Institute of Research, 1977), the animals showed signs of erythema. Skin irritation data are not available for EODA; similar skin irritation effects (transient erythema and desquamation) are expected for EODA.

Table 9 Summary of skin irritation studies (rabbits)

Test substance	Result	Reference
ETP	Desquamation in 1/3 animals exposed to 20 mL/kg bw applied for a 24-hour contact period	Carpenter, C.P., 1959
ESBO	Transient erythema in 4 animals exposed to 20 mL/kg bw applied for a 24-hour contact period	Mellon Institute of Research, 1955; BIBRA, 1988, 1997; and Weil, CS et al., 1963
ELSO	Erythema in 7 animals exposed to 16 mL/kg bw applied for a 24-hour contact period	Carnegie-Mellon Institute of Research, 1977
EODA	No data*	-

* = A similar degree of skin irritation is expected for EODA as that observed for ETP, ESBO and ELSO.

Eye Irritation

There was no evidence of damage when 0.5 mL of ETP was instilled into a rabbits' eye (Weil, CS, et al., 1963). An excess (0.5 ml) of undiluted ESBO was instilled into the conjunctival sac of five rabbit eyes (Mellon Institute of Research, 1955; BIBRA, 1988, 1997; and Weil, CS et al., 1963). There was no damage to the cornea observed. There are no eye irritation data for ELSO or EODA; similar effects (no eye irritation) are expected for ELSO and EODA.

Table 10 Summary of eye irritation studies (rabbits)

Test substance	Result	Reference
ETP	No damage in 5 animals following instillation of .5 mL	Weil, CS, et al., 1963
ESBO	No damage in 5 animals following instillation of .5 mL	Mellon Institute of Research, 1955; BIBRA, 1988, 1997; and Weil, CS et al., 1963
ELSO	No data*	-
EODA	No data*	-

* = A similar degree of eye irritation is expected for EODA and ELSO as that observed for ETP and ESBO.

Studies in Humans

No data available.

Respiratory Tract Irritation

No data available.

3.1.4 Sensitisation

Skin sensitization tests have been conducted with ETP and ESBO. The substances were tested at very dilute concentrations – 0.1%. There is no evidence to consider that these substances are sensitizers but the available tests would not appear to constitute a particularly robust investigation. No data are available for ELSO or EODA; these materials are also not expected to be sensitizers.

Studies in Animals

Skin

A group of twenty male albino guinea pigs were subjected to 8 intracutaneous injections (three per week on alternate days) and topical applications of a 0.1% solution of ETP during 2 1/2 weeks, followed by a 3-week incubation period prior to the challenge dose. Examination for possible sensitization reactions was made 24 and 48 hours thereafter. ETP was negative in the guinea pig sensitization test (Weil, CS et al., 1963).

A group of twenty male albino guinea pigs were subjected to 8 intracutaneous injections (three per week on alternate days) and topical applications of a 0.1% solution of ESBO during 2 1/2 weeks, followed by a 3-week incubation period prior to the challenge dose. Examination for possible sensitization reactions was made 24 and 48 hours thereafter. ESBO was negative in the guinea pig sensitization test (BIBRA, 1988, 1997; Mellon Institute of Research, 1955; and Weil, CS et al., 1963).

Respiratory Tract

No data available.

Studies in Humans

No data available.

Conclusion

Numerous acute toxicity studies have been conducted with ETP, ESBO and ELSO via the dermal and oral route of exposure. A similar order of toxicity is expected for EODA for both dermal and oral exposure. The dermal LD50s of ETP, ESBO and ELSO in rabbits indicate a low order of toxicity, with LD50s ranging from greater than 16 mL/kg bw (ELSO) to greater than 20 mL/kg bw (ETP and ESBO). The oral LD50s of ETP, ESBO and ELSO in rats also indicate a low order of acute toxicity, with LD50 values ranging from14.9 mL/kg bw (ELSO) to greater than 16 mL/kg bw (ETP) up to 41.5 mL/kg bw (ESBO). There are no valid skin irritation studies for any of the EOD materials, however the results from dermal toxicity studies with ETP, ESBO and ELSO indicate no to slight skin irritation; a similar level of skin irritation is expected for EODA. Eye irritation studies have been conducted and indicate no damage is observed following exposure to ETP and ESBO. There are no eye irritation data for ELSO or EODA; similar findings (no eye irritation) are expected for ELSO and EODA. Skin sensitization tests with ESBO and ETP at very dilute concentrations indicate the EOD materials are not sensitizers, but the available tests would not appear to constitute a particularly robust investigation.

3.1.5 Repeated Dose Toxicity

Repeat dose studies by the oral route of exposure (gavage or dietary) have been conducted with ETP and ESBO. Similar studies have not been conducted with EODA and ELSO. EODA and ELSO are expected to have equivalent toxicity to ETP and ESBO because in mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

Studies in Animals

Oral

ETP was administered once daily orally (by gavage) to male rats for at least for 28 days and to female rats throughout the 14 day pre-pairing period, throughout pairing and gestation up to lactation day 4 according to OECD Guideline 422 (RCC, 2005b). The dose levels were 0 (vehicle control), 100, 300 and 1000 mg/kg bw/d. No test article-related mortalities or clinical signs were noted throughout the study. None of the parameters under investigation during the functional observational battery gave any indication of test item-related effects. Neither food consumption nor body weight development was affected by treatment with ETP at any dose level. The assessment of clinical chemistry and hematology parameters indicated no differences between animals treated with ETP and vehicle controls. During necropsy of parent animals no test article- related findings were noted. For males treated at 300 and 1000 mg/kg bw/d, mean absolute and relative liver weights were dose-dependently increased. For females treated at 1000 mg/kg bw/d, mean absolute and relative liver weights were increased. Histopathological findings included the following: Minimal hepatocellular hypertrophy in animals treated at 1000 mg/kg bw/d. This change was considered to represent an adaptive reaction most likely induced by an increased biotransformation of the test article. This was not considered an adverse effect. Increased incidence of minimal follicular cell hypertrophy in the thyroid of animals treated with 1000 mg/kg bw/d. The NOAEL for ETP in this repeat dose toxicity study was considered to be 1000 mg/kg bw/d.

Groups of rats (15/sex) were given diets containing up to 5% ESBO (0, 0.1, 0.5, 1.0, 2.5 or 5% (up to approximately 1.25 g/kg bw/d)) for up to 2 years (BIBRA, 1988, 1997, Larson PS et al., 1960a, and The CP Hall Company, 2002). Five rats/sex/group were sacrificed at 6 months. Organ to body

weight measurements were made for liver, kidney and testes. Blood studies (hemoglobin, red blood cell and differential white cell counts) were made during the eleventh and twenty-fourth months. Histopathology of heart, lung, kidney, spleen, gastroenteric, thyroid, adrenal, pancreas, gonad, muscle and bone marrow tissues was conducted on survivors from the 0, 2.5% and 5% diet groups. Growth appeared to be essentially normal at 2.5%, but appeared to be permanently low in the 5% group. A limited evaluation of the blood (red blood cell and white blood cell counts) revealed no effects. Liver weight was increased in both sexes at 1% and above. There was some evidence that kidney weight was increased in the females at 1% and above. Microscopic examination of the major tissues revealed no cellular changes at 2.5% or 5% (only dose groups examined). The LOAEL was 1% ESBO. In a subchronic study, rats were given diets containing up to 5% ESBO for 15 weeks (Larson PS et al., 1960b). Temporary slowed growth and liver and kidney enlargement at concentrations greater than 1.5% was observed. Liver changes (fatty infiltration) were observed at 2.5% (approximately 1.3 g/kg bw/d) or greater. The LOAEL was greater than 1.5% ESBO. Groups of three dogs were fed up to 5% ESBO (as Paraplex G-60 or G-62) once per day for one year (BIBRA, 1988, 1997, Larson PS et al., 1960a The CP Hall Company, 2002a and 2002b). The dogs were weighed weekly and food intake was monitored. Hematologic studies were made at study initiation, at 6 months and at 12 months. Major tissues were examined microscopically. The dogs were sacrificed at 12 months. Dogs fed 5% Paraplex G-60 or G-62 lost weight. Survival and blood parameters (hemoglobin, red and white blood cell counts) were normal in all treated groups. The major tissues were microscopically normal except for fatty liver changes (fatty infiltration) in one dog given 5% Paraplex G-62. Food intake and body weight were decreased at 5% of either grade. The LOAEL was 5% ESBO. In a 90 day subchronic study, male and female rats were given 0.04, 0.2, 1.0 or 5.0% (5% is approximately 1.25 g/kg bw/d) ESBO (as Plasticizer EPO or Paraplex G-62) in the diet (Carnegie-Mellon Institute of Research, 1976, The CP Hall Company, 2002a, and Mellon Institute of Industrial Research, 1960). There was no effect on body weight gain for treated female rats. Males receiving 5% Plasticizer EPO or Paraplex G-62 had lower body weight gains than controls for the first few weeks of dosing only. Males given 5% Plasticizer EPO ate less diet than the controls. This was the only difference for the male animals given Plasticizer EPO vs. Paraplex G-62. Female animals ate less diet when given either test article at 1% or 5%. Liver weights were increased in rats fed either test article at 5% in diet; this increase was also observed in male rats fed either test article at 1%. There were no test article-related deaths. Gross findings indicated a test article-related effect of Plasticizer EPO on liver and kidney at 1% and 5%. A gross effect on the kidney (male rats at 1% or 5%) and liver (male and female rats at 5%) was observed with Paraplex G-62. The NOAEL was 0.2% ESBO; the LOAEL was 1% ESBO.

Table 11 Summary of repeated dose toxicity

Species	Test substance	Route	Study duration	Doses	LOAEL	NOAEL	Reference
Rat	ETP	Gavage	At least 28 days	0, 100, 300, 1000 mg/kg bw/d	-	1000 mg/kg bw/d	RCC, 2005b
Rat	ESBO	Diet	Up to 2 years	0, 0.1, 0.5, 1.0, 2.5 or 5%	1% (250 mg/kg bw/d)	-	BIBRA, 1988, 1997, Larson PS et al., 1960a, The CP Hall Company, 2002
Rat	ESBO	Diet	15 weeks	Up to 5%	>1.5% (>375 mg/kg bw/d)	-	Larson PS et al., 1960b
Dog	ESBO	Diet	1 year	Up to 5%	5% (1250 mg/kg bw/d)	-	BIBRA, 1988, 1997, Larson PS et al., 1960a, The CP Hall Company, 2002a, 2002b
Rat	ESBO	Diet	90 days	0.04, 0.2, 1.0 or 5.0%	1% (250 mg/kg bw/d)	.2% (50 mg/kg bw/d)	Carnegie-Mellon Institute of Research, 1976, Mellon Institute of Industrial Research, 1960, The CP Hall Company, 2002a
-	EODA	No data *	-	-	-	-	-
-	ELSO	No data *	-	-	-	-	-

* = EODA and ELSO are expected to have equivalent toxicity to ETP and ESBO

Studies in Humans

No data available.

Conclusion

Repeat dose studies by the oral route of exposure (gavage or dietary) have been conducted with ETP and ESBO. The NOAEL for ETP in a standard OECD Guideline 422 (rat) study was considered to be 1000 mg/kg bw/d (the highest dose tested). In a 90 day subchronic study, male and female rats were given 0.04, 0.2, 1.0 or 5.0% (5% is approximately 1.25 g/kg bw/d) ESBO. (Liver weights were increased in rats fed ESBO at 1% or 5% in diet. Gross findings indicated a test article-related effect of ESBO on liver and kidney at 1% and 5%. The NOAEL was 0.2% ESBO; the LOAEL was 1% ESBO. In a 2-year rat feeding study, a LOAEL of 1% ESBO was described based on increased liver and kidney weights. No effects were observed at .5% ESBO. Rats were given diets containing up to 5% ESBO for 15 weeks. Temporary slowed growth and liver and kidney enlargement at concentrations greater than 1.5% was observed. The LOAEL was greater than 1.5% ESBO. Groups of three dogs were fed up to 5% ESBO once per day for one year. Dogs fed 5% ESBO lost weight, and fatty liver changes (fatty infiltration) in one dog given 5% ESBO were observed. Food intake and body weight were decreased at 5% ESBO. The LOAEL was 5% ESBO. The repeated dose toxicity of EODA and ELSO is expected to be similar to that of ETP and ESBO because, in mammalian species these materials are expected to be absorbed and metabolized

in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

3.1.6 Mutagenicity

Bacterial and *in vitro* mammalian cell mutagenicity studies have been conducted with ETP and ESBO.

In vivo Studies

No data available.

In vitro Studies

Gene Mutations. ETP and ESBO are not mutagenic when tested in several strains of *Salmonella* (TA98, TA 100, TA 102, TA1535 and/or TA 1537) or *E. coli* WP2 uvrA in the presence and absence of metabolic activation (BIBRA, 1997; CIBA-GEIGY Ltd., 1988b; Hazelton, 1992a; Monsanto, 1986, 1987a; RCC-CCR, 2005a). ESBO did not induce mutations at the TK locus of L5178Y mouse lymphoma cells in the absence and presence of metabolic activation (BIBRA, 1997 and Hazelton, 1992c). ESBO was negative in a mammalian cell gene mutation assay with CHO cells (HGPRT locus) in the presence or absence of metabolic activation (Monsanto Environmental Health Lab, 1987b). There are no data for EODA or ELSO. The weight of evidence indicates that ETP and ESBO are not mutagenic in bacterial systems. It is anticipated that EODA and ELSO are also not mutagenic in bacterial systems.

Chromosomal Aberrations. ETP did not induce structural chromosome aberrations as determined by the chromosome aberration test in V79 cells (Chinese hamster cell line) in vitro, either in the presence or absence of metabolic activation (RCC-CCR, 2005b). Similarly, ESBO did not induce chromosome aberrations in cultured human peripheral blood lymphocytes when tested to its limit of solubility in both the absence and presence of metabolic activation (BIBRA, 1997 and Hazelton, 1992b). There are no data for EODA or ELSO. The weight of evidence indicates that ETP and ESBO are not mutagenic in mammalian systems. It is anticipated that EODA and ELSO are also not mutagenic in mammalian systems.

Table 12 Summary of genetic toxicity tests

Test type	Strain/species	Test substance	Dose	Conclusion	Reference
Bacterial Gene Mutation	*S typhimurium* TA 98, TA 100, TA 1535, TA 1537 and *E coli* WP2 uvrA	ETP	3, 10, 33, 100, 333, 1000, 2500, and 5000 µg/plate	Negative	RCC-CCR, 2005a
Bacterial Gene Mutation	*S typhimurium* TA98, TA100, TA1535, TA1537 and TA102	ESBO	8, 40, 200, 1000 and 5000 ug/plate (Experiment 1); 312.5, 625, 1250, 2500 and 5000 ug/plate (Experiment 2)	Negative	BIBRA, 1997, Hazelton, 1992a
Bacterial Gene Mutation	*S typhimurium* TA98 and TA100	ESBO	0.03, 0.09, 0.3, 0.9 and 3 mg/plate	Negative	Monsanto, 1986
Bacterial Gene Mutation	*S typhimurium* TA98 and TA100	ESBO	0.5 ml/plate for both organ homogenates and 0.15 ml/plate for small intestine homogenates	Negative	Monsanto, 1987a
Bacterial Gene Mutation	*S typhimurium* TA98, TA100, TA1535, TA1537	ESBO	25, 75, 225, 675, 2025 ug/plate	Negative	BIBRA, 1997, CIBA-GEIGY Ltd., 1988b
Mammalian gene mutation	Mouse lymphoma cells (TK +/- locus of L5178Y)	ESBO	312.5 to 5000 ug/ml (two separate tests)	Negative	BIBRA, 1997, Hazelton, 1992c
Mammalian gene mutation	Hamster CHO cells (HGPRT locus)	ESBO	0.2-2 mg/ml	Negative	Monsanto Environmental Health Lab, 1987b
Chromosome aberration	Chinese hamster V79 cells	ETP	Without S9 mix: 3.1, 6.3, 12.5, 25, 50, 1050, 2100, and 4200 ug/ml; With S9 mix: 3.1, 6.3, 12.5, 25, 50 and 100 ug/ml	Negative	RCC-CCR, 2005b
Chromosome aberration	Human lymphocytes	ESBO	1.554-55 ug/ml	Negative	BIBRA, 1997, Hazelton, 1992b
No data*	-	EODA	-	-	-
No data*	-	ELSO	-	-	-

* = EODA and ELSO are not expected to be mutagenic in bacterial or mammalian systems based on weight of evidence with ETP and ESBO.

Conclusion

No indication of genotoxicity or induction of structural aberrations for the EOD materials is evident in any of the studies conducted. ETP and ESBO did not induce gene mutations in bacteria. ESBO did not induce gene mutations in mouse lymphoma L1578Y TK cells or CHO Cells (HGPRT locus). ETP and ESBO did not induce chromosomal aberrations in cultured mammalian cells. EODA and ELSO are not expected to be mutagenic in bacterial or mammalian systems based on weight of evidence with ETP and ESBO.

3.1.7 Carcinogenicity

Chronic toxicity/carcinogenicity data exist on ESBO; similar studies were not located for ETP, EODA or ELSO. These studies provide compelling data to demonstrate that the EOD materials are not carcinogenic.

In vivo Studies

Chronic/carcinogenicity studies were conducted with ESBO by the oral route (dietary).

Oral

Groups of 48 male and female rats were given up to 2.5% ESBO in the diet for two years (BIBRA, 1986, 1997). Control and SBO treated animals were also run concurrently. The usual parameters for a lifetime toxicity-oncogenicity study were measured. Body weight, food and water consumption, clinical signs of toxic effects, and mortality were followed throughout the study. Hematological and urine samples were collected at selected time points. After 104 weeks, all surviving rats were killed and subjected to a complete gross pathological examination and tissues selected for microscopic examination. There was no adverse effect on survival. The males given 2.5% ESBO gained more weight than the controls, while the females were slightly lighter. The same rats consumed slightly less food than controls, the difference being greater in females than males. The water intake of the females given 2.5% ESBO was lower than the control, especially in the second year of the study. Hematological examination and investigations of urine at 3, 6, 12, 18 and 24 months did not reveal any adverse effects. A lower volume of more concentrated urine was excreted by the females given 2.5% ESBO compared with the controls, with occasional increases in urinary cell excretion. The organ weights in females were similar to controls, while in males given 2.5% ESBO, several organs were heavier than control. This was related to the growth changes since when expressed relative to body weight the value were normal. The incidence of histological findings, including tumors, was similar in treated and control groups. There was a tendency for less severe glomerulonephrosis in the ESBO-treated rats. There was a marginally increased incidence of uterine changes in the females given 2.5% ESBO; since there were similar changes in the females given ESBO, these changes could not be clearly related to ESBO or epoxidation. It was concluded that ESBO was not carcinogenic when fed to rats at up to 2.5% of the diet. Further, it was concluded that the NOAEL was 2.5% providing an average daily intake of approximately 1.0 g/kg in males and 1.4 g/kg in females.

Groups of 15 male and female rats were given ESBO (identified as Paraplex G-60 or G-62) in the diet at 0, 0.1, 0.5, 1.0, 2.5, and 5.0% (BIBRA, 1986, 1988, 1997, Larson PS et al., 1960a). Each group of 15 was subdivided into subgroups of 5 and 10 animals. The groups of 5 were sacrificed at the end of one year (Paraplex G-60) or six months (Paraplex G-62) and subjected to histopathologic studies and organ to body weight measurements (liver, kidney and testes). In addition, animals fed Paraplex G-62 were subjected to blood studies at the 6 months sacrifice. The groups of ten animals were exposed for two years. Blood studies were conducted at 11 and 24 months. Histopathologic studies were conducted on survivors at two years in the 2.5 and 5% dose groups and controls. There

was no definitive effect on survival but there was an early depression of growth at 5% Paraplex G-60. There was no effect of Paraplex G-60 on hematological values. Male rats receiving 5% Paraplex G-60 had significantly elevated liver to body weight ratios. There were no treatment-related histopathologic lesions and there was no evidence of carcinogenicity of Paraplex G-60. There was no definitive effect on survival of Paraplex G-62. Among female rats fed Paraplex G-62, growth was depressed during the early portion of the study, with no effect observed by 8 weeks. There was no effect on hematological values of Paraplex G-62. Females receiving 0.5% Paraplex G-62 and males receiving >2% Paraplex G-62 had significantly elevated liver to body weight ratios. Increased kidney to body weight ratios were observed for females receiving >1.5% Paraplex G-62. There were no treatment-related histopathologic lesions and there was no evidence of carcinogenicity of Paraplex G-62.

Chronic toxicity/carcinogenicity studies have not been conducted with ETP, EODA or ELSO.

Conclusion

ESBO has been assessed for carcinogenicity in two reliable studies by the oral (feed) route of exposure in rats. In both cases, the substances demonstrated no evidence of a carcinogenic response. A similar lack of carcinogenic response is expected for ETP, EODA and ELSO.

3.1.8 Toxicity for Reproduction

Development toxicity and effects on fertility studies are available for ETP and ESBO. Similar studies are not available for EODA and ELSO.

Effects on Fertility

ETP was evaluated for effects on fertility in accordance with OECD Guideline 422 following the protocol previously described in section 3.1.5 (RCC, 205b). The fertility rate was high resulting in at least 9 litters per group for evaluation of reproduction data. There were no treatment-related effects on precoital time, fertility indices, mean duration of gestation, number of implantations, post-implantation loss, pup survival or litter size from birth through to scheduled pup sacrifice on day four post partum at any dose level. No test article-related histopathological findings were noted in the reproductive organs of either sex. In particular, the assessment of the integrity of the spermatogenetic cycle did not reveal any evidence of impaired spermatogenesis. In the absence of any adverse effects on reproductive parameters, the NOAEL (maternal) and NOEL for reproduction was considered to be 1000 mg/kg bw/d.

ESBO was given daily to 3 groups of 28 male and 28 female rats by gavage at dose levels of 0, 100, 300 and 1000 mg/kg bw/d (CIT, 1993b). After 71 days of treatment in males and 15 days of treatment in females, the F0 male and female rats were paired. Each male was paired with one female of the same treatment group until mating occurred or 10 days had elapsed. If no evidence of mating was observed after 10 days, the female was placed after 3 days rest period with another male that had already successfully mated, until mating occurred or 11 days had elapsed. The day when spermatozoa were found was designated as day 0 of pregnancy. Treatment was continued in females during the mating and pregnancy and lactation periods until day 21 post-partum and in males during the mating period until day 21 post-partum of F1 litters. F0 animals were observed daily for clinical signs. The quantity of food consumed by the animals was recorded except during the mating period. Food intake per animal and per day was calculated and body weight was recorded for each males on the first day of treatment (day 1) and then once a week until sacrifice. Body weight was recorded for each females on the first day of treatment (day 1), once a week before mating and during mating periods, on days 0, 7, 14 and 20 of pregnancy, and on days 1, 7, 14 and 21 post-partum. The females were allowed to deliver normally and the F1 litters were examined

daily for clinical signs, viability, physical and reflex development until day 21 post-partum. Pup body weights were recorded on days 1, 4, 7, 14 and 21 post-partum. On day 4 post-partum, the size of each litter was adjusted by eliminating extra pups by random selection, as nearly as possible, at 4 males and 4 females per litter. The number of pups in each litter exhibiting the following characteristics was recorded: on day 5 post-partum: pinna unfolding, hair growth, surface righting reflex on day 11 post-partum: cliff avoidance; on day 13 post-partum: incisor eruption; on day 17 post-partum: eye opening, auricular duct opening, air righting reflex. About 24 hours after the last administration, hematology and blood chemistry investigations were performed in 5 males and 5 females of each group. At the end of the study, macroscopic examination of all F0 males and females and F1 pups was performed. In all the parents, reproductive organs and macroscopic lesions were sampled and additionally in 5 males and 5 females of each group ileum, kidneys and liver were sampled. Microscopic examination of the reproductive organs was performed in all animals of the control and 1000 mg /kg bw/day groups and in animals suspected of infertility, those that died or were sacrificed in the 100 and 300 mg/kg bw/day groups. In addition the livers of one male of the 1000 mg/kg bw/day group and of the control group were also examined microscopically. ESBO did not induce any toxic effects in parent males and females did not disturb their capacity of reproduction and did not impair the development of the F1 offspring. No treatment related mortalities or clinical signs were observed. The mean food consumption and body weight gain of males and females were similar in the control and treated groups. The variations of hematologic or blood chemistry parameters were not of toxicological importance. The macroscopic and microscopic examination of the animals did not reveal any changes attributed to the treatment. The mating and fertility indices of males and females were similar in the control and treated groups. The gestation index and the mean duration of gestation were similar in all groups. The live birth index was 100% in all groups. The viability indices on day 4 and day 21 post-partum, the physical and reflex development of pups and the mean pup body weight were similar in the control and treated groups. Under the experimental conditions, the highest tested dose of 1000 mg/kg bw/d was found to be the NOEL.

In a range-finding study, groups of 12 male and 12 female rats were given ESBO at doses of 150, 450, and 1000 mg/kg bw/d by gavage (CIT, 1993a). Treatment began 15 days before mating and continued through mating and pregnancy for half the female animals. Treatment continued through lactation and until day 7 post-partum of F1 litters for the other half of the females. Treatment continued for the males through day 7 post-partum. F0 animals were observed daily for clinical signs. Food consumption and body weights were measured at designated intervals. On day 20 of pregnancy, half the females per group were sacrificed, examined macroscopically and fetuses removed by caesarean section. Litter parameters included number of corpora lutea, implantation sites, resorptions, dead and live fetuses. Fetuses were weighed, sexed and examined. The other females were allowed to deliver normally, and F1 litters were examined daily for clinical signs and viability until day 7 post-partum. Pup body weights were recorded on days 1, 4 and 7 post-partum. At the end of the study, macroscopic examination of all F0 males and females and F1 pups was performed. Daily administration of ESBO up to 1000 mg/kg bw/d did not induce any toxic effect in parent male or female animals did not disturb their capacity for reproduction and did not impair development of the F1 offspring.

Developmental Toxicity

ETP was evaluated for developmental toxicity in accordance with OECD Guideline 422 following the protocol previously described in section 3.1.5 (RCC, 205b). No test article-related abnormal findings were noted for pups at first litter check or during the first four days post partum. Sex ratios at first litter check and on day 4 post partum were unaffected by treatment. Mean pup weights on day 0 and day 1 post partum were unaffected by treatment with the test item. Mean pup weight development during the first 4 days post partum was unaffected by treatment with the test article.

There were no test article-related macroscopic findings noted during necropsy of F1 pups. In the absence of any adverse effects, the NOAEL and NOEL for developmental toxicity was considered to be 1000 mg/kg bw/d.

ESBO was administered by gavage to pregnant female rats from day 6 to day 15 of pregnancy at the dose levels of 0, 100, 300 and 1000 mg/kg bw/d (CIT, 1993c, BIBRA 1997). Clinical signs including signs of abortion and mortality were checked daily. The quantity of food consumed was measured at specified intervals and food intake per animal and per day was calculated. Body weight was recorded for each female on days 2, 6, 9, 12, 15 and 20 of pregnancy. On day 20 of pregnancy, the females were sacrificed, examined macroscopically and fetuses removed by Caesarean section. The litter parameters were recorded: number of corpora lutea, implantation sites, resorptions, dead and live fetuses. The dams were submitted to a macroscopic examination of the main organs (heart, lung, liver, kidneys, stomach, and intestines). Fetuses were weighed, sexed and submitted to external, soft tissue and skeletal examinations. The soft tissue findings were classified into malformations and anomalies. The skeletal findings were classified into skeletal variations, anomalies and malformations. ESBO was well tolerated by the dams at all the dose levels. No clinical signs, no deaths and no abortions were noted in any of the groups. The mean food consumption and body weight gain of the females with completed pregnancy were similar in the control and treated groups. No treatment-related macroscopic changes were observed at necropsy of the females. The mean number of corpora lutea, implantation sites, live fetuses, the post-implantation loss and fetal body weight were similar in the control and treated groups. The pre-implantation loss was higher in each treated group when compared to the control one. The rate of resorptions was similar in the control and treated groups. No external malformations were observed in fetuses of the control or treated groups. No treatment-related soft tissue anomalies or malformations were noted in fetuses of any group. No dose-related effects were noted on the incidence of the skeletal variations, anomalies or malformations.

In a range-finding study, groups of 12 male and 12 female rats were given ESBO at doses of 0, 150, 450 and 1000 mg/kg bw/d by gavage (CIT, 1993a). Treatment began 15 days before mating and continued through mating and pregnancy for half the female animals. Treatment continued through lactation and until day 7 post-partum of F1 litters for the other half of the females. Treatment continued for the males through day 7 post-partum. F0 animals were observed daily for clinical signs. Food consumption and body weights were measured at designated intervals. On day 20 of pregnancy, half the females per group were sacrificed, examined macroscopically and fetuses removed by caesarean section. Litter parameters included number of corpora lutea, implantation sites, resorptions, dead and live fetuses. Fetuses were weighed, sexed and examined. The other females were allowed to deliver normally, and F1 litters were examined daily for clinical signs and viability until day 7 post-partum. Pup body weights were recorded on days 1, 4 and 7 post-partum. At the end of the study, macroscopic examination of all F0 males and females and F1 pups was performed. Daily administration of ESBO up to 1000 mg/kg bw/d did not induce any toxic effect in parent male or female animals did not disturb their capacity for reproduction and did not impair development of the F1 offspring.

Table 13 Summary of reproductive toxicity

Species	Substance	Exposure period/Route	Doses	NOAEL Maternal	NOAEL Fetal	Reference
Rat	ETP	Continuous/Gavage	0, 100, 300 and 1000 mg/kg bw/d	1000 mg/kg bw/d	1000 mg/kg bw/d	RCC, 2005b
Rat	ESBO	Continuous/Gavage	0, 100, 300 and 1000 mg/kg bw/d	1000 mg/kg bw/d	1000 mg/kg bw/d	CIT, 1993b

Species	Substance	Exposure period/Route	Doses	NOAEL Maternal	NOAEL Fetal	Reference
Rat	ESBO	Continuous/Gavage	150, 450, and 1000 mg/kg bw/d	1000 mg/kg bw/d	1000 mg/kg bw/d	CIT, 1993a
Rat	ESBO	Day 6 to day 15	0, 100, 300 and 1000 mg/kg bw/d	1000 mg/kg bw/d	1000 mg/kg bw/d	CIT, 1993c, BIBRA 1997
No data	EODA	-	-	-	-	-
No data	ELSO	-	-	-	-	-

Conclusion

ETP and ESBO have been evaluated for the potential to cause developmental toxicity in rats and were not teratogenic, nor did they demonstrate reproductive toxicity. Based on the lack of reproductive toxicity or developmental effects with ETP and ESBO, EODA and ELSO are not expected to cause developmental toxicity or to demonstrate reproductive toxicity.

3.2 Initial Assessment for Human Health

Numerous acute toxicity studies have been conducted with ETP, ESBO and ELSO via the dermal and oral route of exposure. Acute toxicity studies were not available for EODA. The dermal LD50s of ETP, ESBO and ELSO in rabbits indicate a low order of toxicity, with LD50s ranging from greater than 16 mL/kg bw (ELSO) to greater than 20 mL/kg bw (ETP and ESBO). The oral LD50s of ETP, ESBO and ELSO in rats also indicate a low order of acute toxicity, with LD50 values ranging from14.9 mL/kg bw (ELSO) to greater than 16 mL/kg bw (ETP) up to 41.5 mL/kg bw (ESBO). A similar order of toxicity is expected for EODA. There are no valid skin irritation studies for any of the EOD materials, however the results from dermal toxicity studies with ETP, ESBO and ELSO indicate no to slight skin irritation. Skin irritation data are not available for EODA; similar skin irritation effects (transient erythema and desquamation) are expected for EODA. Eye irritation studies have been conducted and indicate no damage is observed. There are no eye irritation data for ELSO or EODA; similar effects (no eye irritation) are expected for ELSO and EODA. Skin sensitization tests with ESBO and ETP at very dilute concentrations indicate the EOD materials are not sensitizers, but the available tests would not appear to constitute a particularly robust investigation.

Repeat dose studies by the oral route of exposure (gavage or dietary) have been conducted with ETP and ESBO. The NOAEL for ETP in a standard OECD Guideline 422 (rat) study was considered to be 1000 mg/kg bw/d (the highest dose tested). In multiple repeat dose toxicity studies with rats, the lowest $NOAEL_{liver\ and\ kidney}$ was 0.2% ESBO and the lowest $LOAEL_{liver\ and\ kidney}$ was 1% ESBO. Groups of three dogs were fed up to 5% ESBO once per day for one year. Dogs fed 5% ESBO lost weight, and fatty liver changes (fatty infiltration) in one dog given 5% ESBO were observed. Food intake and body weight were decreased at 5% ESBO. The LOAEL was 5% ESBO. The repeated dose toxicity of EODA and ELSO is expected to be similar to that of ETP and ESBO because, in mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

In vitro, ETP and ESBO were negative in bacterial or mammalian gene mutations assays. ETP and ESBO did not induce chromosomal aberrations in Chinese hamster V79 or human lymphocyte cells. EODA and ELSO are not expected to be mutagenic in bacterial or mammalian systems based on the lack of mutagenicity of ETP and ESBO.

Chronic/carcinogenicity studies were conducted with ESBO by the oral route (dietary). These studies provide compelling data to demonstrate that the EOD materials are not carcinogenic. ESBO was not carcinogenic when fed to rats at up to 2.5% of the diet. Further, the NOAEL was 2.5% providing an average daily intake of approximately 1.0 g/kg bw in males and 1.4 g/kg bw in females. There were no treatment-related histopathologic lesions and there was no evidence of carcinogenicity of ESBO in groups of male and female rats given ESBO in the diet at 0, 0.1, 0.5, 1.0, 2.5, and 5.0%. A similar lack of carcinogenic response is expected for ETP, EODA and ELSO.

ETP and ESBO have been evaluated for the potential to cause developmental toxicity in rats and were not teratogenic, nor did they demonstrate reproductive toxicity. In a standard OECD Guideline 422 rat study with ETP, there were no adverse effects on reproductive parameters, and the NOAEL (maternal) and NOEL for reproduction was considered to be 1000 mg/kg bw/d. Daily administration of ESBO up to 1000 mg/kg bw/d did not induce any toxic effect in parent male or female animals, did not disturb their capacity for reproduction and did not impair development of the F1 offspring. Based on the lack of reproductive toxicity or developmental effects with ETP and ESBO, EODA and ELSO are not expected to cause developmental toxicity or to demonstrate reproductive toxicity.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Based on the physicochemical properties of the category members (low water solubility and log Kow values >6.2), acute aquatic toxicity endpoints are not relevant, as the substances are unlikely to be bioavailable to aquatic organisms in acute aquatic testing. Rather, a chronic Daphnia study with the most water soluble category member (EODA) was proposed.

Acute Toxicity Test Results

Acute toxicity tests with fish (48 hr) as well as tests with both freshwater and marine crustacea (24 hr), and algae (72 hr) have been conducted with ESBO. Although the fish and invertebrate studies were conducted for shorter time periods than currently specified in the OECD guidelines, for the time periods examined there was no or minimal evidence of toxicity observed at the limit of water solubility. In the algae study with ESBO, on the basis of biomass, the median effective concentration was 72 h EbC50 > 8 mg/L and 72 h NOEC = 2.3 mg/L. Effects are not expected to be observed below the water solubility of these materials. Based on the physicochemical properties of the category members (very low water solubility, and log Kow values >6.2, and readily biodegradable), further acute aquatic toxicity testing is not warranted, as the substances are unlikely to be bioavailable to aquatic organisms.

Chronic Toxicity Test Results

A chronic daphnia study using EODA was proposed. During the study pre-work to prepare a water accommodated fraction (WAF) of EODA it became apparent that phase separation could not be achieved through settling or centrifugation and it would be necessary to filter the test solutions to remove un-dissolved test material. Non-dissolved material present in test media has the potential to exert physical effects on test organisms, which are unrelated to toxicity. Following the OECD recommended procedures for preparation of a WAF, aqueous mixtures of the test substance were prepared in daphnid culture water at loadings of 1, 10, and 100 mg/L (three replicates per loading) (RCC, 2005c). The mixtures were gently stirred for seven days, and then filtered through a 0.2 µm filter. Regardless of the loading concentration, all filtrates of these mixtures appeared clear, and no un-dissolved material was revealed using the Tyndall effect. Therefore, two replicates from each loading were analyzed for dissolved test substance using a derivatization GC-MS method. No

substance-specific peak was detected in any of the chromatograms for analysis of the WAF solutions. The limit of detection was 0.02 mg/L. Recoveries for spiked water samples over the range of 0.5 mg/L to 10 mg/L were between 69% and 84%. It appears that the true solubility of the substance in daphnia medium is below 0.02 mg/L, and therefore analytical confirmation of test concentrations and test substance stability in the test medium would not be possible. There was no water-soluble test substance detected above 0.02 mg/L in a WAF prepared from a loading of 100 mg/L. The water solubility value is different than that reported elsewhere in the SIAR, SIAP, and IUCLID and is likely due to presence of undissolved (micro-emulsion) test substance remaining in the water-soluble solutions. Therefore, considering the structure and low water solubility of the test substance, it was concluded that the WAF is not likely to exert measurable effects on daphnids, and a test would not provide meaningful, quantitative information on such effects. Further laboratory investigation of the chronic toxicity of this substance to aquatic organisms is therefore deemed not necessary.

It is the nature of these EOD materials to form an unstable dispersion of liquid test substance droplets (microemulsion) in aqueous media. It was demonstrated that these suspended droplets cannot be completely separated from the bulk solution phase by centrifugation alone. This was confirmed in the attempts to prepare appropriate WAFs of the test substance, which did not contain dissolved test substance at above the method detection limit of 0.02 mg/L. The option of conducting the chronic daphnia test with another member of the EOD family was considered, however similar results are expected from the WAF preparations for these poorly soluble substances. Considerable investment was made to develop an analytical method, which is capable of detecting sub-mg/L concentrations of test substance dissolved in water. Further enhancements of the method were not expected to achieve significantly lowered detection limits.

Toxicity to Microorganisms

No data available.

4.2 Terrestrial Effects

No data available.

4.3 Other Environmental Effects

No data available.

4.4 Initial Assessment for the Environment

The melting point of the EOD materials range from <-23.2 to -2.2 C. All the EOD materials decompose at 176 – 204C, boiling points are not applicable. The estimated water solubilities of the EOD materials range from 0.937 to 6.65 mg/L. It is the nature of the EOD materials to form an emulsion upon mixing in water. They do not dissolve and they do not remain as individual molecules in solution, which reflects the difficulty with which the undissolved microemulsion is separated from true aqueous solution. The actual water solubilities of the EOD substances are lower than reported. The log Kow values of these substances are estimated to be greater than 6.2 according to the OECD Guideline No. 117:HPLC Method. The vapor pressures of the EOD materials are less than 0.005 hPa. The reported vapor pressure values are presumed to reflect the influence of minor impurities having relatively low boiling points. Estimated half-lives for the indirect photolysis in the atmosphere range from (approximately) 2 to 5 hours for the four materials.

Abiotic hydrolysis of these materials is slow in part due to the low water solubility of the materials; the hydrolysis half-life for ETP is greater than one year while the half-life of ESBO could not be determined. Level III Fugacity modeling, using loading rates for air, soil, and water of 1000 kg/h for each media, shows the primary distribution to sediment (ranging from 29-36%) and soil (ranging from 63-67%). Biodegradation studies with ETP and ESBO indicate that these materials are readily biodegradable (70% within 28 days; OECD 301F test). ETP exhibited 70% degradation within 28 days in the OECD 301F test, whereas ESBO exhibited > 79% degradation over 28 days in the OECD 301B test. Previous studies showed lesser extents of biodegradation for these substances (21% of ETP, 0% of ESBO after 20 days). The discrepancy in results among these biodegradation studies can be attributed to differences in inoculum density, and more importantly, the degree to which the insoluble test substance is dispersed in the aqueous test mixtures. Based on data from ETP and ESBO, the EOD category is expected to be readily biodegradable. Whereas the estimated log Kow value of > 6.2 indicates a high potential for bioaccumulation of these substances, their uptake into fish is expected to be hindered by their large molecular size. If taken up by fish, these carboxylate ester-containing substances are expected to be readily metabolized and excreted. Thus, the bioaccumulation potential is expected to be much lower than predicted from log Kow alone.

Acute toxicity tests with fish (48 hr), as well as tests with both freshwater and marine crustacea (24 hr), and algae (72 hr) have been conducted with ESBO. Although the fish and invertebrate studies were conducted for shorter time periods than currently specified in the OECD guidelines, for the time periods examined there was no or minimal evidence of toxicity observed at the limit of water solubility. In the algae study with ESBO, on the basis of biomass, the median effective concentration was 72 h EbC50 > 8 mg/L and 72 h NOEC = 2.3 mg/L. Effects are not expected to be observed below the water solubility of these materials. Based on the physicochemical properties of the category members (very low water solubility, log Kow values >6.2, and readily biodegradable), the substances are unlikely to be bioavailable to aquatic organisms in acute aquatic testing. In preparation to conduct a chronic daphnia study it was demonstrated that there was no water soluble test substance detected above 0.05 mg EODA/L in a Water Accomodated Fraction (WAF) prepared from a loading of 100 mg/L. Therefore, considering the structure and low water solubility of EODA, it was concluded that the WAF is not likely to exert acute measurable effects on daphnids, and a chronic test would not be likely to provide meaningful, quantitative information on such effects. The option of conducting the chronic daphnia test with another member of the EOD family was considered, however similar results are expected from the WAF preparations for these poorly soluble substances. Further laboratory investigation of the chronic toxicity of this substance to aquatic organisms is therefore deemed not necessary.

5 RECOMMENDATIONS

Human Health: The chemicals are currently a low priority for further work as they do not possess properties indicating a hazard for human health.

Environment: The chemicals are currently a low priority for further work as they do not possess properties indicating a hazard for the environment.

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I U C L I D

Data Set

Existing Chemical	:	ID: 61789-01-3
CAS No.	:	61789-01-3
EINECS Name	:	Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters
EC No.	:	263-024-2

Producer related part

Company	:	Epona Associates, LLC
Creation date	:	28.10.2002

Substance related part

Company	:	Epona Associates, LLC
Creation date	:	28.10.2002
Status	:	
Memo	:	EOD
Printing date	:	30.05.2006
Revision date	:	
Date of last update	:	30.05.2006
Number of pages	:	173
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

Comment : Category Justification

Remark : This category consists of related fatty acid esters. ETP is a monoester with 2-ethylhexanol. EODA is a diester with propylene glycol. ESBO and ELSO are triesters with glycerol (triglycerides). These materials are considered a category for purposes of environmental and health hazard screening assessments because of the similarities metabolism of these materials in microbial, aquatic and mammalian systems. Uptake of any member of this category by microorganisms, aquatic species or mammals is expected to result in quite rapid metabolism by esterases. Carboxylesterases have been demonstrated to be present in many families of fish and aquatic invertebrates as well as mammals (Miller et al., 1981, Sugihara et al., 1994, Escartin and Porte, 1997 and Barron et al., 1999). The action of the esterase will result in a mixture of epoxidized fatty acids and 2-ethylhexanol from ETP, epoxidized fatty acids and propylene glycol from EODA, and epoxidized fatty acids and glycerol from ESBO and ELSO. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

In mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides.

Lipase is an enzyme that assists in the breakdown and digestion of fat in the body. Pancreatic lipase works at the oil/water interface since triglycerides are insoluble. During metabolism in the GI tract, pancreatic lipase preferentially hydrolyzes triglycerides to release the free fatty acids from the SN-1 and SN-3 (terminal) positions of the glycerol backbone. Other products of metabolism are mono- and diglycerides. The monoglycerides, diglycerides, and fatty acids can be absorbed (World Health Organization, 1974)

In a similar manner, pancreatic lipase and other digestive enzymes have been shown to hydrolyze propylene glycol monoesters and diesters in vitro. The absorption, metabolism and hydrolysis of propylene glycol distearate

(which is structurally similar to EODA) were studied in rats using isotopically labelled compounds. These processes for the propylene glycol esters were found to be similar to those of the glycerol esters. So, there is evidence that the propylene glycol esters of fatty acids are hydrolyzed to propylene glycol and fatty acids. (World Health Organization, 1967)

The ETP structure is similar to that of the monoglycerides, formed from the ELSO and ESBO. Further hydrolysis can also occur via carboxylesterase activity.

Hydrolysis data for 61789-01-3 (ETP) is considered to be representative of 68609-92-7 (EODA), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Biodegradation, genetic toxicity, repeated dose, reproductive and developmental data for 61789-01-3 (ETP) and 8013-07-8 (ESBO) are considered to be representative of 68609-92-7 (EODA) and 8016-11-3 (ELSO). The chronic daphnia data for 68609-92-7 (EODA) are considered to be representative of 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Acute toxicity data for 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO), are considered to be representative of 68609-92-7 (EODA).

06.01.2006 (17) (18)

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	= 100 % w/w
Colour	:	yellowish
Odour	:	faint

24.11.2003 (6)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2-Ethylhexanol, tall oil fatty acids epoxidized ester

06.11.2002

2-Ethylhexyl epoxytallates

06.11.2002

Drapex 4.4

06.09.2005

Expoxidized 2-ethylhexyl ester of tall oil fatty acid

06.11.2002

Fatty acid, tall oil, epoxidized, 2-ethylhexyl ester

06.11.2002

Fatty acids, tall oil, epoxidized, 2-ethylhexyl esters

06.11.2002

Fatty acids, tall-oil, 2-ethylhexyl esters, epoxidized

06.11.2002

Flexol EP-8

06.11.2002

sec-Octyl epoxytallate

06.11.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 453 - 4536 tonnes produced in 2002

22.09.2005

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : use
Category :

Remark : ETP is used in flexible low temperature PVC application such as refrigerator gaskets

06.01.2006 (2)

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	:	< -23.2 °C
Sublimation	:	
Method	:	OECD Guide-line 102 "Melting Point/Melting Range"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The pour point was determined using BS 2000: Part 15 (equivalent to ISO 3016), Method 102 of the OECD Guidelines. A pour point was considered more appropriate than a freezing point determination for this test material since it became moderately viscous during cooling and was a complex mixture containing oil. Pour point procedures are considered more appropriate for oil based materials and mixtures.
Result	:	The pour point of the test material was determined to be < 250 +/- 3 K (-23.15 degrees C).
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

31.10.2002 (13)

2.2 BOILING POINT

Decomposition	:	yes
Method	:	OECD Guide-line 103 "Boiling Point/boiling Range"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The determination was carried out by differential scanning calorimetry (DSC) using the procedure specified in ASTM E537-86, Method 103 of the OECD Guidelines.
Remark	:	From data obtained in the vapor presure study (SafePharm Laboratories Project Number 166/002), the boiling point of the test material was estimated to be 643 K (369.85 degrees C) at 101.325 kPa (10.1325 hPa).
Result	:	The test material has been determined to decompose from approximately 449 K (175.85 degrees C) at 102.00 kPa (1020 hPa). As the test material decomposed, no value for boiling point could be determined.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

07.11.2002 (13)

2.3 DENSITY

Type	:	density
Value	:	= .92 g/cm³ at 25 °C
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Internal company data
18.05.2006 (7)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : < .001 hPa at 25 °C
Decomposition :
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : The test material did not change in appearance under the conditions used in the determination.
Result : Vapour pressure was 8.8 x 10-7 Pa at 25 deg C. (Pa/100 = hPa)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
07.05.2003 (14)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : > 6.2 at °C
pH value :
Method : OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : The partition coefficient of the test material has been determined to be >1.59 x 10+6, log 10 Pow > 6.2. Substances having a log10 Pow greater than 3 are regarded as having the potential to bioaccumulate in the environment.
Test condition : The standard used was DDT. The pH of the mobile phase was adjusted to 3 to assure that the test substance was tested in non-ionized form.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.05.2004 (13)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = .00297 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description : slightly soluble (0.1-100 mg/L)
Stable :

Deg. product	:	
Method	:	OECD Guide-line 105
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	(2) It is the nature of these EOD materials to form an emulsion upon mixing in water. They do not dissolve and they do not remain as individual molecules in solution, which reflects the difficulty with which the undissolved microemulsion is separated from true aqueous solution. This was confirmed in the attempts to prepare appropriate water accommodated fractions (WAF) of EODA (CAS number 68609-92-7), which did not contain dissolved test substance at or above the method detection limit of 0.05 mg/L. These results from the WAF preparation suggest that actual water solubility of the EOD substances are lower than reported above.
Result	:	The water solubility of the test material has been determined to be 2.97 x 10-3 g/l of solution at 20 +/- 0.5 degrees C. The range was 2.59 x 10 -3 to 3.26 x 10 -3 g/l.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

18.05.2004 (13)

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

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 4.5 hour(s)
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	
Rate constant	:	= .0000000000286081 cm³/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	other (calculated): AopWIN (v1.90)
Year	:	2002
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Result :

Atmospheric Oxidation (25 deg C) [AopWin v1.90]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 30.2514 E-12 cm3/molecule-sec
Half-Life = 0.354 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 4.243 Hrs
Individual Structure Results:

ETPL:
CIS-isomer:
OVERALL OH Rate Constant = 138.0909 E-12 cm3/molecule-sec
Half-life = 0.929 Hrs (12-hr day; 1.5E6 OH/cm3)
TRANS-isomer:
OVERALL OH Rate Constant= 153.2909 E-12 cm3/molecule-sec
Half-Life = 0.837 Hrs (12-hr day; 1.5E6 OH/cm3)

ETPO:
CIS-isomer:
OVERALL OH Rate Constant = 84.9960 E-12 cm3/molecule-sec
Half-Life = 1.510 Hrs (12-hr day; 1.5E6 OH/cm3)
TRANS-isomer:
OVERALL OH Rate Constant = 92.5960 E-12 cm3/molecule-sec
Half-Life = 1.386 Hrs (12-hr day; 1.5E6 OH/cm3)

ETPOE:
OVERALL OH Rate Constant = 29.8406 E-12 cm3/molecule-sec
Half-Life = 0.358 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 4.301 Hrs

Test substance	:	SMILES code = CCCCC(CC)COC(=O)CCCCCCCC1OC1CCCCCCCC
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

18.05.2004 (1)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 1 year at 25 °C
t1/2 pH7	:	> 1 year at 25 °C
t1/2 pH9	:	>= 1 year at 25 °C
Deg. product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	In a further assessment at a physiological important pH and temperature (pH 1.2, 37 degrees C), 85.1% of the test material was found to remain after 24 hours.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

31.10.2002 (13)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: EPIWIN (v3.05)
Year	:	2002
Result	:	Level III Fugacity Model: Mass Amount Half-Life Emissions (percent) (hr) (kg/hr) Air 8.02e-006 8.49 0 Water 7.3 360 1000 Soil 27.9 360 1000 Sediment 64.8 1.44e+003 0 Persistence Time: 92
Test substance	:	SMILES code = CCCCC(CC)COC(=O)CCCCCCCC1OC1CCCCCCCC
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

03.10.2005 (8)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	activated sludge, domestic
Concentration	:	123 mg/l related to Test substance related to
Contact time	:	28 day(s)
Degradation	:	= 70 (±) % after 28 day(s)
Result	:	other: biodegradable
Kinetic of testsubst.	:	10 day(s) = 30 - 36 % 14 day(s) = 39 - 45 % 28 day(s) = 69 - 72 % % %
Control substance	:	Benzoic acid, sodium salt
Kinetic	:	14 day(s) = 84 - 85 % 28 day(s) = 87 - 89 %
Deg. product	:	no
Method	:	OECD Guide-line 301 F "Ready Biodegradability: Manometric Respirometry Test"
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : EU Commission Directive 92/69 EEC, C.4-D, Manometric Respirometry Test, 1992. Since the test article is a low density, poorly water soluble liquid, the test article was adsorbed onto silica gel followed by dispersion into the test water. The method of addition is based on ISO 10634 (1995). The percent biodegradation of the test item was calculated based on the chemical oxygen demand (COD) of 2.72 mg O2/mg test item.

Result : The biochemical oxygen demand (BOD) of ETP in the test media significantly increased from Day 1 until test-termination after 28 days. At the end of the 28-day exposure period, the mean biodegradation of ETP amounted to 70%.

Thus, ETP was found to be biodegradable under the conditions of the test within 28 days.

In its purest commercially available form, the test item (epoxidized oil) consists of a mixture of similar structures having slightly differing chain lengths and degree of epoxidation. A forthcoming revision to the OECD Guidelines for Testing Chemicals indicates that the 10 day window should not be applied to interpretation of ready biodegradability test results for mixtures of structurally similar chemicals, such as oils and surfactants (OECD Draft revised Introduction to Section 3 of the OECD Test Guidelines: Biodegradation and Bioaccumulation, July 2003 version). In tests of such substances, a sequential biodegradation of the individual components is anticipated, leading to inaccurate quantitation of the degradation rate for individual structures (Richterich, K., Steber, J. (2001): The time window - an inadequate criterion for ready biodegradability assessment of technical surfactants.

Chemosphere 44: 1649-1654). Therefore, the 10-day window is not applied in assessing the ready biodegradability of this test substance.

No degradation of the test item occurred in the abiotic control under the conditions of the test.

In the toxicity control, containing both ETP and the reference item sodium benzoate, no inhibitory effect of the test item on the biodegradation was determined. Thus, ETP had obviously no inhibitory effect on the activity of activated sludge microorganisms at the tested concentration of approximately 100 mg/L.

In the procedure controls, the reference item sodium benzoate was degraded by an average of 84% until Day 14. The average biodegradation of the reference item was 88% at the end of the test (Day 28), thus confirming suitability of the activated sludge.

Test substance : Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters, 100% pure
Reliability : (1) valid without restriction
Guideline study
Flag : Critical study for SIDS endpoint
20.01.2006 (10)

Type : aerobic
Inoculum : other bacteria:Polybac POLYSEED
Contact time :
Degradation : = 21 (±) % after 20 day(s)
Result : other: not readily biodegradable
Deg. product :
Method :
Year : 1996
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Methods used were published in Standard Methods for the Examination of Water and Wastewater. Am Public Health Assoc., 17th Ed., Washington, DC (1989) and Price, K.S., Waggy, G.T., Conway, R.A. (Jan 1974). Brine Shrimp Assay and Seawater BOD of Petrochemicals.
The test inoculum was a commercially available lyophilized bacterial seed (Polybac POLYSEED). This product is a blend containing a broad spectrum of bacterial species formulated to degrade both municipal and industrial wastes.
Remark : Based on the lack of study details the conclusion of "inherently biodegradable" cannot be confirmed.
Result : The 5-, 10- and 20-day biooxidation values were 6%, 13% and 21%, respectively.
Reliability : (2) valid with restrictions
20.01.2006 (4)

Deg. product :
Method : other: modeling
Year : 2002
GLP :
Test substance : as prescribed by 1.1 - 1.4

Result : Probability of Rapid Biodegradation (BIOWIN v4.00):

Linear Model : 0.5957
Non-Linear Model : 0.8197
Expert Survey Biodegradation Results:
Ultimate Survey Model: 3.0198 (weeks)
Primary Survey Model : 4.0126 (days)
Readily Biodegradable Probability (MITI Model):
Linear Model : 0.7499
Non-Linear Model : 0.7045

Reliability : (2) valid with restrictions
21.11.2002 (3)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : 375
Elimination :
Method : other
Year : 2002
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Taken alone, the estimated log Kow > 6.2 indicates a high potential for bioaccumulation according the TGD. Using the non-linear QSAR recommended for substances having log Kow > 6, a log BCF value of 4.6 is estimated. However, substances having molecular weight > 700 Daltons are considered to have low bioaccumulation potential, due to steric hindrance of membrane permeation.
If taken up into fish, these fatty acid ester substances are expected to be rapidly metabolized and excreted. Due to their demonstrated potential for rapid metabolism in fish, the category of linear aliphatic fatty acid esters have recently been categorized by Environment Canada as having low potential to bioaccumulate.

Result : BCF Program (v2.15) Results:
MILES : CCCCC(CC)COC(=O)CCCCCCCC1OC1CCCCCCCCCHEM
MOL FOR: C26 H50 O3
MOL WT : 410.69

Bcfwin v2.15
Log Kow (estimated) : 10.08 Log Kow (experimental): not available from database
Log Kow used by BCF estimates: 6.20 (user entered) Equation Used to Make BCF estimate: Log BCF = 0.77 log Kow - 0.70 + Correction
Correction(s): Value Alkyl chains (8+ -CH2- groups) -1.500
Estimated Log BCF = 2.574 (BCF = 375)

Reliability : (2) valid with restrictions
Modeled data
30.05.2006 (8)

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	:	> 16 ml/kg bw
Species	:	rat
Strain	:	other:albino
Sex	:	male
Number of animals	:	20
Vehicle	:	no data
Doses	:	
Method	:	other
Year	:	1959
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 male albino rats were dosed with 8, 16, 32 or 64 ml/kg and followed for 14 days. The method of moving average was used to calculate the LD50.
Result	:	All animals dosed with 8 or 16 ml/kg survived the entire 14 day period. All animals dosed with 32 ml/kg died 1-3 days after dosing. At the highest dose level, all rats died 1-2 days after dosing. Rats that died at 32 and 64 ml/kg had congested lungs, mottled or pale livers, pale kidney surfaces with congested interiors and slightly congested adrenals.
Test substance	:	Plasticizer EP-8; Epoxidized 2-ethylhexy ester of tall oil fatty acid; composition not available
Reliability	:	(2) valid with restrictions

18.05.2004 (5)

Type	:	LD50
Value	:	= 22.6 ml/kg bw
Species	:	rat
Strain	:	other:Carworth-Wistar
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	other
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Epoxidized 2-ethylhexy ester of tall oil fatty acid
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

18.05.2004 (16)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	other:saturated vapor
Value	:	
Species	:	rat

Strain	:	no data
Sex	:	female
Number of animals	:	6
Vehicle	:	
Doses	:	
Exposure time	:	8 hour(s)
Method	:	other
Year	:	1959
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 6 female rats were exposed to a near saturated vapor for 8 hours. The saturated vapor was generated by passing 2.5 lpm of air through a fritted glass disc immersed in 50 ml of test material. Animals were observed for 14 days following exposure.
Remark	:	The approximate concentration of the saturated vapor is not known.
Result	:	All animals survived.
Test substance	:	Plasticizer EP-8; Epoxidized 2-ethylhexy ester of tall oil fatty acid; composition not available
Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meet important criteria of today's standard methods.

19.07.2005 (5)

Type	:	other
Value	:	
Species	:	rat
Strain	:	no data
Sex	:	female
Number of animals	:	6
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	other
Year	:	1959
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 6 female rats were exposed to mists and vapors of test material for 1, 2 or 4 hours. Aerosol was generated by passing air at 2.5 lpm through a fritted glass disc immersed in 50 ml of test material which was in a bath held at 170C.
Remark	:	Degradation has been reported to occur at 176 deg C. Thus these animals were probably exposed to degradation products from the test material. The identity of the degradation products is not known. The approximate concentration of the saturated vapor is not known. These details are not needed as this study does not fulfill a critical SIDS endpoint.
Result	:	All rats died following 4 hour exposure to the test material. Four of six rats died following 2 hour exposure to the test material. All animals exposed to the test material for one hour survived.
Test substance	:	Plasticizer EP-8; Epoxidized 2-ethylhexy ester of tall oil fatty acid; composition not available
Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meet important criteria of today's standard methods.

18.05.2004 (5)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 20 ml/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	3
Vehicle	:	
Doses	:	
Method	:	other
Year	:	1959
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of three male albino New Zealand rabbits were dosed with 20 ml/kg of neat test material. Animals were 3-5 months of age and averaged 2.5 kg in weight. They were immobilized during the 24 hour skin contact period. Vinylite sheeting was used to retain the dose in contact with clipped skin during this time period. After the 24 hour contact period, the test material was removed and the animals were observed for a 14-day observation period. The moving average method was used to calculate the LD50.
Result	:	All animals survived a 24-hr dose of 20 ml/kg. One rabbit had desquamation but the other two had no skin reaction.
Test substance	:	Plasticizer EP-8; Epoxidized 2-ethylhexy ester of tall oil fatty acid; composition not available
Reliability	:	(2) valid with restrictions

01.12.2003 (5)

Type	:	LD50
Value	:	> 20 ml/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	4
Vehicle	:	no data
Doses	:	
Method	:	
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Epoxidized 2-ethylhexy ester of tall oil fatty acid
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

18.05.2004 (16)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted

Exposure	:	Open
Exposure time	:	24 hour(s)
Number of animals	:	5
Vehicle	:	
PDII	:	
Result	:	slightly irritating
Classification	:	
Method	:	other
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Five rabbits received 0.01 ml undiluted test material to theuncovered, clipped skin of the belly.
Remark	:	An irritation score of "2" was assigned by the study author. Under the more severe conditions of the dermal toxicity study (20 ml applied for a 24-hour contact period) conducted with three rabbits, one rabbit had desquamation but the other two rabbits showed no skin reactions.
Test substance	:	Epoxidized 2-ethylhexy ester of tall oil fatty acid
Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meetimportant criteria of today's standard methods (only 0.01 ml used).

19.07.2005 (16)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	.5 ml
Exposure time	:	
Comment	:	
Number of animals	:	5
Vehicle	:	
Result	:	not irritating
Classification	:	
Method	:	other
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A corneal injury score of "1" was assigned by the study author. There was no evidence of damage.
Test substance	:	Epoxidized 2-ethylhexy ester of tall oil fatty acid
Reliability	:	(2) valid with restrictions

19.07.2005 (16)

5.3 SENSITIZATION

Type	:	other:sensitization test
Species	:	guinea pig
Number of animals	:	20
Vehicle	:	
Result	:	not sensitizing
Classification	:	
Method	:	other
Year	:	1963

GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of twenty male albino guinea pigs were subjected to 8 intracutaneous injections (three per week on alternate days) and topical applications of a 0.1% solution during 2 1/2 weeks, followed by a 3-week incubation period prior to the challenge dose. Examination for possible sensitization reactions was made 24 and 48 hours thereafter.
Remark	:	This is similar to the Guinea Pig Maximization test except that an adjuvant was not used.
Test substance	:	Epoxidized 2-ethylhexy ester of tall oil fatty acid
Conclusion	:	Test material was negative in the guinea pig sensitization test.
Reliability	:	(2) valid with restrictions

05.08.2005 (16)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-acute
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	Males: at least 28 days. Females: 14 days prior to pairing, throughout pregnancy until postnatal day 4
Frequency of treatm.	:	daily
Post exposure period	:	
Doses	:	0, 100, 300 and 1000 mg/kg bw/d
Control group	:	yes, concurrent vehicle
NOAEL	:	= 1000 mg/kg bw
Method	:	other: OECD Guideline 422
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	ETP was administered once daily orally (by gavage) to males at least for 28 days (including 14 days prepairing) and to female rats throughout the 14 day prepairing period and throughout pairing and gestation up to lactation day 4. The dose levels were 0 (vehicle control), 100, 300 and 1000 mg/kg bw/d. A standard dose volume of 2 mL/kg body weight with a daily adjustment to the actual body weight was used. Control animals were dosed with vehicle alone (corn oil).
Result	:	No test article-related mortalities or clinical signs were noted throughout the study. None of the parameters under investigation during the functional observational battery gave any indication of test item-related effects. Neither food consumption nor body weight development was affected by treatment with the test article at any dose level. The assessment of clinical chemistry and hematology parameters indicated no differences between animals treated with test article and vehicle controls. During necropsy of parent animals no test article-realted findings were noted. For males treated at 300 and 1000 mg/kg bw/d, mean absolute and relative liver weights were dose-dependently increased. For females treated at 1000 mg/kg bw/d, mean absolute and relative liver weights were increased. Histopathological findings included the following:

LIVER: Minimal hepatocellular hypertrophy in animals treated at 1000 mg/kg bw/d. This change was considered to represent an adaptive reaction most likely induced by an increased biotransformation of the test article. This was not considered an adverse effect.
THYROID: Increased incidence of minimal follicular cell hypertrophy in animals treated with 1000 mg/kg bw/d.

Test substance : Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters, 100% pure
Conclusion : The NOAEL was considered to be 1000 mg/kg bw/d.
Reliability : (1) valid without restriction
Guideline study
Flag : Critical study for SIDS endpoint
19.07.2005 (9)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Bacterial reverse mutation assay
System of testing : S typhimurium TA 98, TA 100, TA 1535, TA 1537 and E coli WP2 uvrA
Test concentration : 3; 10; 33; 100; 333; 1000; 2500; and 5000 µg/plate
Cycotoxic concentr. : >5000 ug/plate
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 471
Year : 2005
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Commission Directive 2000/32/EC, L1362000, Annex 4D", dated May 19, 2000.

This study was performed to investigate the potential of Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP) to induce gene mutations in the plate incorporation test (Experiment I) and the pre-incubation test (Experiment II) using the Salmonella typhimurium strains TA 1535, TA 1537, TA 98, and TA 100, and the Escherichia coli strain WP2 uvrA.

To evaluate the toxicity of the test item a pre-experiment was performed with strains TA 1535, TA 1537, TA 98, TA 100, and WP2 uvrA. Eight concentrations (3-5000 ug/plate) were tested for toxicity and mutation induction with three plates each. The experimental conditions in this Pre-Experiment were the same as described below for the Experiment I (plate incorporation test). The pre-experiment is reported as Experiment I since no relevant toxic effects were observed and 5000 ug/plate was chosen as the maximal concentration.

The assay was performed in two independent experiments both with and without liver microsomal activation. Each concentration, including the controls, was tested in triplicate. The test item was tested at the following concentrations:

Experiment I: 3; 10; 33; 100; 333; 1000; 2500; and 5000 µg/plate
Experiment II: 33; 100; 333; 1000; 2500; and 5000 µg/plate

Result : Experiment I
Without Activation: Revertant Colony Counts (Mean ± SD)

Dose Level	TA 1535		TA 1537		TA 98	TA 100	WP2 uvrA
Ethanol	30±6	16±3	34±7	125±22	52±6		
Untreated	27±1	11±3	36±6	112±16	58±7		
ETP 3 ug	24±9	16±4	32±6	96±14	52±6		
ETP 10 ug	32±3	15±6	37±12	101±9	53±5		
ETP 33 ug	28±7	14±3	39±3	97±2	53±6		
ETP 100 ug	32±4	15±1	31±8	108±15	54±6		
ETP 333 ug	21±8	11±1	43±6	101±11	60±8		
ETP 1000 ug	28±6	14±3	44±4	96±3	56±8		
ETP 2500 ug	24±8	17±5	37±3	91±13	51±3		
ETP 5000 ug	29±8	8±3	30±2	89±13	43±5		
NaAz 10ug	1515±45		2313±104				
NOPD 10 ug			412±30				
NOPD 50 ug		80±7					
MMS 4.0 uL					1546±102		

With Activation: Revertant Colony Counts (Mean ± SD)

Ethanol	42±7	25±7	54±9	109±4	65±6		
Untreated	31±5	28±10	51±6	115±13	61±3		
ETP 3 ug	31±6	23±4	58±8	98±4	61±6		
ETP 10 ug	34±3	27±4	54±6	117±8	68±10		
ETP 33 ug	37±1	25±3	61±6	101±6	71±2		
ETP 100 ug	36±5	25±4	56±3	120±25	64±10		
ETP 333 ug	44±4	25±5	73±9	108±8	66±4		
ETP 1000 ug	38±13	22±2	64±12	122±6	63±7		
ETP 2500 ug	38±5	24±3	56±8	117±15	61±16		
ETP 5000 ug	38±3	16±5	50±4	79±4	41±4		
2-AA 2.5 ug	412±43	237±12	1971±104	2486±152			
2-AA 10 ug					284±26		

NaAz = Sodium azide
NOPD = 4-nitro-o-phenylene-diamine
MMS = Methyl methane sulfonate
2-AA = 2-Aminoanthracene

Experiment II

Without Activation: Revertant Colony Counts (Mean ± SD)

Dose Level	TA 1535		TA 1537		TA 98	TA 100	WP2 uvrA
Ethanol	22±6	7±1	32±5	146±11	68±12		
Untreated	19±3	14±8	27±4	162±13	56±12		
ETP 33 ug	19±5	10±4	35±5	130±23	59±7		
ETP 100 ug	16±0	14±1	32±6	137±11	68±18		
ETP 333 ug	27±4	13±3	31±8	141±27	64±8		
ETP 1000 ug	16±7	13±1	33±8	138±18	69±11		
ETP 2500 ug	21±6	12±5	32±3	157±6	73±7		
ETP 5000 ug	24±3	12±7	37±6	121±14	59±10		
NaAz 10ug	1664±58		2194±199				
NOPD 10 ug			377±11				
NOPD 50 ug		87±4					
MMS 4.0 uL					370±112		

With Activation: Revertant Colony Counts (Mean ± SD)

Ethanol	26±6	12±3	48±5	165±24	75±14		
Untreated	25±4	16±3	48±3	163±7	68±6		
ETP 33 ug	26±2	14±2	54±6	155±14	63±3		
ETP 100 ug	18±4	16±2	47±10	152±4	84±4		
ETP 333 ug	26±2	14±5	56±1	134±13	82±4		
ETP 1000 ug	29±4	19±5	47±6	146±24	76±5		
ETP 2500 ug	26±6	17±2	45±6	150±14	63±4		
ETP 5000 ug	20±9	12±5	36±4	129±12	65±4		
2-AA 2.5 ug	397±9	464±34	3592±112	3872±101			
2-AA 10 ug					301±19		

NaAz = Sodium azide
NOPD = 4-nitro-o-phenylene-diamine
MMS = Methyl methane sulfonate
2-AA = 2-Aminoanthracene
The plates incubated with the test item showed normal background growth up to 5000 µg/plate with and without metabolic activation in both independent experiments.

No toxic effects, evident as a reduction in the number of revertants, occurred in the test groups with and without metabolic activation.

No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP) at any dose level, neither in the presence nor absence of metabolic activation (S9 mix). There was also no tendency for higher mutation rates with increasing concentrations in the range below the generally acknowledged border of biological relevance.

Appropriate reference mutagens were used as positive controls and showed a distinct increase of induced revertant colonies.

Test substance : Purity: 100%
Conclusion : It can be stated that during the described mutagenicity test and under the experimental conditions reported, the test item did not induce gene mutations by base pair changes or frameshifts in the genome of the strains used.

Therefore, Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP) is considered to be non-mutagenic in this Salmonella typhimurium and Escherichia coli reverse mutation assay.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
05.05.2005 (12)

Type : Cytogenetic assay
System of testing : Chinese hamster V79 cells
Test concentration : Without S9 mix: 3.1, 6.3, 12.5, 25, 50, 1050, 2100, and 4200 (approx. 10 mM) ug/ml; With S9 mix: 3.1, 6.3, 12.5, 25, 50 and 100 (conc. exhibiting clear test item precipitation) ug/ml
Cycotoxic concentr. : Without S9 mix: 4200 ug/ml; With S9 mix: no relevant cytotoxicity
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 473
Year : 2005
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Commission Directive 2000/32/EC, L1362000, Annex 4A: "Mutagenicity - In vitro Mammalian Chromosome Aberration Test", dated May 19, 2000.

This in vitro test was performed to assess the potential of Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP; diluted in ethanol) to induce structural chromosome aberrations. Evaluation of cytogenetic damage induced in V79 cells (cell line from the lung of the Chinese Hamster)

in the absence and the presence of metabolic activation was performed in two independent experiments at one preparation interval (18 hrs) in Experiment I and at two preparation intervals (18 hrs and 28 hrs) in Experiment II, according to the following design:

Experiment I (without S9 mix):
Exposure period: 4 hrs
Recovery: 14 hrs
Preparation interval: 18 hrs

(with S9 mix):
Exposure period: 4 hrs
Recovery: 14 hrs
Preparation interval: 18 hrs

Experiment II (without S9 mix):
Exposure period: 18 or 28 hrs
Recovery: -
Preparation interval: 18 or 28 hrs

(with S9 mix):
Exposure period: 4 hrs
Recovery: 24 hrs
Preparation interval: 28 hrs

A pre-test on cell growth inhibition with 4 hours and 24 hours treatment was performed in order to determine the toxicity of the test item using concentrations between 32.8 and 4200 (approx. 10 mM) ug/ml. In the pre-test on toxicity, precipitation of the test item after 4 hours treatment was observed at 32.8 ug/ml and above in the absence and the presence of S9 mix. Using reduced cell numbers as an indicator for toxicity in the pre-test, clear toxic effects were observed after 4 hours treatment with 4200 ug/ml in the absence of S9 mix; therefore, 4200 ug/ml was chosen as the top concentration in Experiment 1 in the absence of S9 mix. Since no relevant toxicity was observed in the pre-test on toxicity in the presence of S9 mix, the test item was tested up to a concentration exhibiting clear test item precipitation as recommended in OECD 473; therefore, 100 ug/ml was chosen as the top concentration in Experiment I in the presence of S9 mix. Dose selection of Experiment II was also influenced by test item toxicity and the occurrence of the test item precipitation. In the range-finding experiment no clearly reduced cell numbers were observed after 24 hours exposure with 4200 ug/ml. However, based on the data after 4 hours exposure, 4200 ug/ml was chosen as top treatment concentration for continuous exposure in the absence of S9 mix. In the presence of S9 mix 100 ug/ml was chosen as top treatment concentration in Experiment II with respect to recommendations of OECD 473.

In the chromosome aberration assay, two parallel cultures were set up in each experiment group. Cells were treated with the test substance from 3.1 to 4200 ug/mL for 4, 18 or 28 hours (without activation) or with 3.1 to 100 ug/mL for 4 hours (with activation); all cells were harvested at 18 or 28 hours after treatment initiation. Following treatment 100

plates were scored for structural chromosome aberrations.

EMS was used as a positive control in the non-activated study, CPA was used as the positive control in the activated study. The solvent (ethanol) was used as the solvent control, both with and without activation.

Result : Exp. I; Prep interval 18 hrs; Exp period 4 hrs with S9 mix

Test Item (ug/ml)	Polyploid Cells (%)	Cell # (%)Cntrl	Mitotic Indices (%)	Aberrant cells Incl. Gaps*	Excl. Gaps*	With Exch
Negative	2.4	n.t.	100	2.5	2.0	1.0
Solvent-1	1.8	100	100	1.5	1.5	0.0
Positive-2	2.4	n.t.	96	11.5	11.5s	5.0
12.5	1.7	96	96	2.5	2.0	0.0
25.0	1.7	94	100	3.5	3.5	1.5
50.0p	1.0	87	92	5.0	3.0	1.5
Exp. II; Prep interval 28 hrs; Exp period 4 hrs with S9 mix						
Negative	1.5	n.t.	100	3.5	3.0	1.0
Solvent-1	1.1	100	100	1.0	1.0	0.0
Positive-2	1.8	n.t.	105	10.0	9.5s	3.0
25.0	1.0	109	112	1.5	1.0	0.0
50.0	1.6	69	113	1.0	0.5	0.5
100.0p	2.3	70	104	2.0	1.5	0.0

*Inclusive cells carrying exchanges
**Cell count on spread slides
n.t. Not tested
P = precipitation occurred
S = Aberration frequency statistically significant higher than corresponding control values
1 = Ethanol 0.5% (v/v)
2 = CPA 1.0 ug/ml

In Experiment I in the absence of S9 mix no toxic effects indicated by reduced mitotic indices or reduced cell numbers were observed after treatment with the test item. Cytotoxicity indicated by reduced cell numbers of about and below 50% of control was observed in Experiment II, after 18 and 28 hours continuous treatment in the absence of S9 mix. Since no relevant toxicity was observed in the pre-test on toxicity in the presence of S9 mix, the test item was tested up to a concentration exhibiting clear test item precipitation as recommended in the OECD Guideline 473.

In both independent experiments, neither a statistically significant nor a biologically relevant increase in the number of cells carrying structural chromosomal aberrations was observed after treatment with the test item.

No relevant increase in the frequencies of polyploid metaphases was found after treatment with the test item as compared to the frequencies of the controls.

Appropriate mutagens were used as positive controls. They induced statistically significant increases ($p<0.05$) in cells with structural chromosomes aberrations.

Exp. I; Prep interval 18 hrs; Exp period 4 hrs w/o S9 mix

Test Item (ug/ml)	Polyploid Cells (%)	Cell # (%)Cntrl	Mitotic Indices (%)	Aberrant cells Incl. Gaps*	Excl. Gaps*	With

Test Item (ug/ml)	Polyploid Cells (%)	(%)Cntrl	Cell # Mitotic Indices (%)	Aberrant cells Incl. Gaps*	Excl. Gaps*	With Exch
Negative	0.9	n.t.	100	1.0	0.0	0.0
Solvent-1	2.2	100**	100	1.0	1.0	0.0
Positive-2	1.7	n.t.	99	12.5	11.0s	5.0
6.3	1.8	90**	88	2.0	1.5	1.0
12.5	2.6	80**	101	2.0	0.5	0.0
25.0	2.2	105**	102	2.5	2.5	1.0
Exp. II; Prep interval 18 hrs; Exp period 18 hrs w/o S9 mix						
Negative	1.7	n.t.	100	2.5	1.0	0.0
Solvent-1	1.6	100	100	1.0	0.0	0.0
Positive-3	1.3	n.t.	106	18.5	15.5s	4.0
12.5	1.7	89	120	1.5	1.5	0.0
25.0	1.8	106	110	1.0	0.0	0.0
50.0p	1.9	115	145	1.0	0.0	0.0
4200p	2.6	49	116	3.5	1.5	0.5
Exp. II; Prep interval 28 hrs; Exp period 28 hrs w/o S9 mix						
Negative	0.7	n.t.	100	1.5	0.5	0.0
Solvent-1	0.7	100	100	0.5	0.5	0.0
Positive-3	1.0	n.t.	47	9.5	9.5s	4.0
12.5	2.2	128	141	0.5	0.5	0.0
25.0	1.2	87	108	0.0	0.0	0.0
50.0p	1.6	93	170	0.5	0.0	0.0
4200.0p	1.6	52	136	2.0	1.0	0.0

*Inclusive cells carrying exchanges
**Cell count on spread slides
n.t. Not tested
P = precipitation occurred
S = Aberration frequency statistically significant higher than corresponding control values
1 = Ethanol 0.5% (v/v)
2 = EMS 300.0 ug/ml
3 = 200.0 ug/ml

Exp. I; Prep interval 18 hrs; Exp period 4 hrs with S9 mix

Test Item (ug/ml)	Polyploid Cells (%)	(%)Cntrl	Cell # Mitotic Indices (%)	Aberrant cells Incl. Gaps*	Excl. Gaps*	With Exch
Negative	2.4	n.t.	100	2.5	2.0	1.0
Solvent-1	1.8	100	100	1.5	1.5	0.0
Positive-2	2.4	n.t.	96	11.5	11.5s	5.0
12.5	1.7	96	96	2.5	2.0	0.0
25.0	1.7	94	100	3.5	3.5	1.5
50.0p	1.0	87	92	5.0	3.0	1.5
Exp. II; Prep interval 28 hrs; Exp period 4 hrs with S9 mix						
Negative	1.5	n.t.	100	3.5	3.0	1.0
Solvent-1	1.1	100	100	1.0	1.0	0.0
Positive-2	1.8	n.t.	105	10.0	9.5s	3.0
25.0	1.0	109	112	1.5	1.0	0.0
50.0	1.6	69	113	1.0	0.5	0.5
100.0p	2.3	70	104	2.0	1.5	0.0

*Inclusive cells carrying exchanges
**Cell count on spread slides
n.t. Not tested
P = precipitation occurred
S = Aberration frequency statistically significant higher than corresponding control values
1 = Ethanol 0.5 (v/v)
2 = CPA 1.0 ug/ml

Test substance	:	Purity: 100%
Conclusion	:	It can be stated that under the experimental conditions reported, the test item did not induce structural chromosome aberrations as determined by the chromosome aberration test in V79 cells (Chinese hamster cell line) in vitro. Therefore, Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP) is considered to be non-clastogenic in this chromosome aberration test with and without S9 mix when tested up to cytotoxic and/or precipitating concentrations.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

19.07.2005 (11)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

Species	:	mouse
Sex	:	
Strain	:	C3H
Route of admin.	:	dermal
Exposure period	:	up to 27 months
Frequency of treatm.	:	three days per week
Post exposure period	:	none: exposure occured until animal died
Doses	:	One brushfull of undiluted test article/application
Result	:	negative
Control group	:	
Method	:	other
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Hair was removed with electric clippers, as needed, from the backs of a group of 90-day old mice. Three applications per week of one brushfull of test article was applied to the midline of the back on Monday, Wednesday and Friday. Observations for papillomas and carcinomas were made during each painting period. Groups of 30 to 40 mice were used. The mice were observed until death.
Result	:	There were 30, 23 and 6 animals alive at 12, 17 and 24 months, respectively. No skin tumors were observed.
Test substance	:	Epoxidized 2-ethylhexy ester of tall oil fatty acid
Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meet important criteria of today's standard methods.

18.05.2004 (15) (16)

5.8.1 TOXICITY TO FERTILITY

Type	:	One generation study
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	Males: 28 days; Females: 14 d prepairing, throughout pairing and gestation up to post natal day 4

Frequency of treatm.	:	daily
Premating exposure period		
Male	:	14 d
Female	:	14 d
Duration of test	:	
No. of generation studies	:	1
Doses	:	0, 100, 300, 1000 mg/kg bw/d
Control group	:	yes, concurrent vehicle
NOAEL parental	:	= 1000 mg/kg bw
NOAEL F1 offspring	:	= 1000 mg/kg bw
Result	:	No effect on fertility
Method	:	OECD combined repeated dose and reproductive/developmental toxicity screening test
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	ETP was administered once daily orally (by gavage) to males at least for 28 days (including 14 days prepairing) and to female rats throughout the 14 day prepairing period and throughout pairing and gestation up to lactation day 4. The dose levels were 0 (vehicle control), 100, 300 and 1000 mg/kg bw/d. A standard dose volume of 2 mL/kg body weight with a daily adjustment to the actual body weight was used. Control animals were dosed with vehicle alone (corn oil).
Result	:	The fertility rate was high resulting in at least 9 litters per group for evaluation of reproduction data. There were no treatment-related effects on precoital time, fertility indices, mean duration of gestation, number of implantations, post-implantation loss, pup survival or litter size from birth through to scheduled pup sacrifice on day four post partum at any dose level. No test article related histopathological findings were noted in the reproductive organs of either sex. In particular, the assessment of the integrity of the spermatogenetic cycle did not reveal any evidence of impaired spermatogenesis.
Test substance	:	Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters, 100% pure
Conclusion	:	In the absence of any adverse effects on reproductive parameters, the NOAEL and NOEL for reproduction was considered to be 1000 mg/kg bw/d.
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint

19.07.2005 (9)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	Males: 28 days; Females: 14 days prepairing throughout pairing and gestation and up to postnatal day 4
Frequency of treatm.	:	daily
Duration of test	:	
Doses	:	0, 100, 300 and 1000 mg/kg bw/d
Control group	:	yes, concurrent vehicle

NOAEL maternal tox.	:	= 1000 mg/kg bw
NOAEL teratogen.	:	= 1000 mg/kg bw
Result	:	no effect on developmental parameters
Method	:	other: OECD Guideline 422
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	ETP was administered once daily orally (by gavage) to males at least for 28 days (including 14 days prepairing) and to female rats throughout the 14 day prepairing period and throughout pairing and gestation up to lactation day 4. The dose levels were 0 (vehicle control), 100, 300 and 1000 mg/kg bw/d. A standard dose volume of 2 mL/kg body weight with a daily adjustment to the actual body weight was used. Control animals were dosed with vehicle alone (corn oil).
Result	:	No test article-related abnormal findings were noted for pups at first litter check or during the first four days post partum. Sex ratios at first litter check and on day 4 post partum were unaffected by treatment. Mean pup weights on day 0 and day 1 post partum were unaffected by treatment with the test item. Mean pup weight development during the first 4 days post partum was unaffected by treatment with the test article. There were no test article-related macroscopic findings noted during necropsy of F1 pups.
Test substance	:	Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters, 100% pure
Conclusion	:	In the absence of any adverse effects, the NOAEL and NOEL for developmental toxicity was considered to be 1000 mg/kg bw/d.
Reliability	:	(1) valid without restriction Guideline study
Flag	:	Critical study for SIDS endpoint

19.07.2005 (9)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

(1) AopWin (v1.90) (2002)

(2) Arkema (2005) Personal Communication

(3) BIOWIN (v4.00) and MITI Model (2002)

(4) Bloss, T.B. (1996) Biodegradation testing data on Flexol Plasticizer EP-8. Unpublished report of Union Carbide Corporation. January 31, 1996.

(5) Carpenter, C.P. (1959) Range-finding tests on Plasticizer EP-8. Unpublished report 22-32 of Union Carbide Corporation.

(6) Crompton (2003) Material Safety Data Sheet Drapex (R) 4.4 Revision: 1.5 09/30/2003.

(7) Crompton Corporation (2005) Personal Communication

(8) EPIWIN (v3.05) (2002)

(9) RCC (2005) Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP) Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test in the Rat. RCC Study number 855892. June 21, 2005.

(10) RCC (2005) Ready Biodegradability of Fatty Acids, Tall-Oil, Epoxidized, 2-Ethylhexylesters (ETP) in a Manometric Respirometry Test. RCC Study Number 855890.

(11) RCC-CCR (2005) In vitro Chromosome Aberration Test in Chinese Hamster V79 Cells with Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP). RCC-CCR Study Number 848602. February 15, 2005.

(12) RCC-CCR (2005) Salmonella typhimurium and Escherichia coli Reverse Mutation Assay with Fatty acids, tall-oil, epoxidized, 2-ethylhexylesters (ETP). RCC-CCR Study Number 848601. February 21, 2005.

(13) Safepharm Laboratories (2002) Determination of General Physico-chemical Properties, SafePharm Laboratories, Project Number 1666/001.

(14) Safepharm Laboratories (2002) Determination of Vapour Pressure, SafePharm Laboratories, Project Number 1666/002.

(15) Weil, C.S. (1961) Studies on Carcinogenesis. Unpublished report of Union Carbide 24-117.

(16) Weil, CS, Condra, N, Haun, C and Streigel, JA. (1963) Experimental carcinogenicity and acute toxicity of representative epoxides. American Industrial Hygiene Assoc. Journal Vol 24, 305-325, 1963.

(17) World Health Organization (1967) Toxicological Evaluation Of Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases, FAO Nutrition Meetings, Report Series No. 40A,B,C, WHO/Food Add./67.29, 1967

(18) World Health Organization (1974) WHO FOOD ADDITIVES SERIES NO. 5 Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. Geneva 1974

I U C L I D

Data Set

Existing Chemical	:	ID: 68609-92-7
CAS No.	:	68609-92-7
EINECS Name	:	9-Octadecenoic acid (Z)-, epoxidized, ester with propylene glycol
EC No.	:	271-842-6

Producer related part

Company	:	Epona Associates, LLC
Creation date	:	28.10.2002

Substance related part

Company	:	Epona Associates, LLC
Creation date	:	28.10.2002
Status	:	
Memo	:	EOD
Printing date	:	30.05.2006
Revision date	:	
Date of last update	:	30.05.2006
Number of pages	:	172
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

Comment : Category Justification

Remark : This category consists of related fatty acid esters. ETP is a monoester with 2-ethylhexanol. EODA is a diester with propylene glycol. ESBO and ELSO are triesters with glycerol (triglycerides). These materials are considered a category for purposes of environmental and health hazard screening assessments because of the similarities metabolism of these materials in microbial, aquatic and mammalian systems. Uptake of any member of this category by microorganisms, aquatic species or mammals is expected to result in quite rapid metabolism by esterases. Carboxylesterases have been demonstrated to be present in many families of fish and aquatic invertebrates as well as mammals (Miller et al., 1981, Sugihara et al., 1994, Escartin and Porte, 1997 and Barron et al., 1999). The action of the esterase will result in a mixture of epoxidized fatty acids and 2-ethylhexanol from ETP, epoxidized fatty acids and propylene glycol from EODA, and epoxidized fatty acids and glycerol from ESBO and ELSO. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

In mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides.

Lipase is an enzyme that assists in the breakdown and digestion of fat in the body. Pancreatic lipase works at the oil/water interface since triglycerides are insoluble. During metabolism in the GI tract, pancreatic lipase preferentially hydrolyzes triglycerides to release the free fatty acids from the SN-1 and SN-3 (terminal) positions of the glycerol backbone. Other products of metabolism are mono- and diglycerides. The monoglycerides, diglycerides, and fatty acids can be absorbed (World Health Organization, 1974)

In a similar manner, pancreatic lipase and other digestive enzymes have been shown to hydrolyze propylene glycol monoesters and diesters in vitro. The absorption, metabolism and hydrolysis of propylene glycol distearate (which is structurally similar to EODA) were studied in rats

using isotopically labelled compounds. These processes for the propylene glycol esters were found to be similar to those of the glycerol esters. So, there is evidence that the propylene glycol esters of fatty acids are hydrolyzed to propylene glycol and fatty acids. (World Health Organization, 1967)

The ETP structure is similar to that of the monoglycerides, formed from the ELSO and ESBO. Further hydrolysis can also occur via carboxylesterase activity.

Hydrolysis data for 61789-01-3 (ETP) is considered to be representative of 68609-92-7 (EODA), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Biodegradation, genetic toxicity, repeated dose, reproductive and developmental data for 61789-01-3 (ETP) and 8013-07-8 (ESBO) are considered to be representative of 68609-92-7 (EODA) and 8016-11-3 (ELSO). The chronic daphnia data for 68609-92-7 (EODA) are considered to be representative of 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Acute toxicity data for 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO), are considered to be representative of 68609-92-7 (EODA).

06.01.2006 (10) (11)

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	9-Octadecenoic acid (9Z)-, epoxidized, ester with propylene glycol
Smiles Code	:	
Molecular formula	:	
Molecular weight	:	
Petrol class	:	

06.09.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	= 100 % w/w
Colour	:	
Odour	:	

24.11.2003 (3)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

9-Octadecenoic acid (Z)-, epoxidized, ester with propylene glycol

06.11.2002

Oleic acid, 1,2-propylene glycol epoxidized ester

06.11.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 453 - 4536 tonnes produced in 2002

22.09.2005

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : use
Category :

Remark : EODA is a high monomeric epoxy plasticizer which offers low volatility, low temperature flexibility and high compatibility in polyvinyl chloride systems. EODA is used in ysemi-rigid and flexible vinyl formulations, vinyl plastisol and organosols, coated fabrics and automotive interiors and moldings. EODA is primarily used to keep plastics and rubber soft and pliable in flooring, upholstery, food packaging, hoses, tubing, blood bags and other products. The epoxy functionality provides excellent heat and light stability.

18.05.2006 (2)

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	:	= -4.2 °C
Sublimation	:	
Method	:	OECD Guide-line 102 "Melting Point/Melting Range"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Freezing Temperature (based on Method BS4633: Method for the Determination of Crystallizing Point)
Remark	:	A freezing point determination was considered most appropriate since the test material is only slightly viscous at ambient temperature. A definitive freezing point was obtained.
Result	:	The material became increasingly viscous during cooling until the freezing point. The freezing point of the test material has been determined to be 269 +/- 0.5 K (-4.15 degrees C)
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

07.11.2002 (8)

2.2 BOILING POINT

Decomposition	:	yes
Method	:	OECD Guide-line 103 "Boiling Point/boiling Range"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The determination was carried out by differential scanning calorimetry (DSC) using the procedure specified in ASTM E537-86, Method 103 of the OECD Guidelines.
Remark	:	From data obtained in the vapour pressure study (SafePharm Laboratories Project Number 1666/004), the boiling point of the test material is estimated to be 827 K (553.85 degrees C) at 101.79 kPa (10.179 hPa).
Result	:	The test material has been determined to decompose from approximately 477 K (203.85 degrees C) at 101.79 kPa (10.179 hPa). As a result of this, no value for the boiling point could be determined.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

07.11.2002 (8)

2.3 DENSITY

Type	:	density
Value	:	= .949 - .9551 g/cm³ at 25 °C
Method	:	other
Year	:	2005
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Internal company data
18.05.2006 (2)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = .005 hPa at 25 °C
Decomposition :
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : In the quantity used, the test material prior to testing appeared as a clear colorless liquid. After test was completed, the test sample was a clear, extremely pale yellow liquid.
Result : Vapor pressure = 5.0 x 10-6 Pa at 25 degrees C
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.05.2004 (9)

2.5 PARTITION COEFFICIENT

Partition coefficient :
Log pow : > 6.2 at °C
pH value :
Method : OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : The partition coefficient of the test material has been determined to be > 1.59 x 10+6, log 10 Pow > 6.2. Substances having a log10 Pow greater than 3 are regarded as having the potential to bioaccumulate in the environment.
Test condition : The standard used was DDT. The pH of the mobile phase was adjusted to 3 to assure that the test substance was tested in non-ionized form.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
07.11.2002 (8)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : < .02 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :

Stable	:	
Deg. product	:	
Method	:	other
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	(2) It is the nature of these EOD materials to form an emulsion upon mixing in water. They do not dissolve and they do not remain as individual molecules in solution, which reflects the difficulty with which the undissolved microemulsion is separated from true aqueous solution. This was confirmed in the attempts to prepare appropriate water accommodated fractions (WAF) of EODA (CAS number 68609-92-7), which did not contain dissolved test substance at or above the method detection limit of 0.05 mg/L. These results from the WAF preparation suggest that actual water solubility of the EOD substances are lower than reported above.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

16.11.2005 (6)

Solubility in	:	Water
Value	:	= .00665 g/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	slightly soluble (0.1-100 mg/L)
Stable	:	
Deg. product	:	
Method	:	OECD Guide-line 105
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The preliminary water solubility test indicated that the column elution method should have been performed as the solubility was less than 1 x 10 -2 g/l. However, due to the physical nature of the test material, it was not possible to use this method. Experience has shown that coating of liquid test materials onto glass beads causes these beads to adhere together, forming a plug within the column which prevents water circulation.
Result	:	The water solubility of the test material has been determined to be 6.65 x 10-3 g/l of solution at 20 +/- 0.5 degrees C. The range was determined to be 5.67 to 7.49 x 10 -3 g/l.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

18.05.2004 (8)

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

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 3 hour(s)
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	
Rate constant	:	= .0000000000424033 cm³/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	other (calculated): AopWIN
Year	:	2002
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Atmospheric Oxidation (25 deg C) [AopWin v1.90]: Hydroxyl Radicals Reaction: OVERALL OH Rate Constant = 42.4033 E-12 cm3/molecule-sec Half-Life = 0.252 Days (12-hr day; 1.5E6 OH/cm3) Half-Life = 3.027 Hrs
Test substance	:	SMILES = 2CCCCCC1OC1CC2OC2CCCCCCCC(=O)OC(C)COC(=O)CCCCCCCC3OC3CCCCCCC C
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

18.05.2004 (1)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	> 1 year at 25 °C
t1/2 pH7	:	> 1 year at 25 °C
t1/2 pH9	:	= 1 year at 25 °C
Deg. product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2002
GLP	:	yes
Test substance	:	other TS
Result	:	In a further assessment at a physiological important pH and temperature (pH 1.2, 37 degrees C), 85.1% of the test material was found to remain after 24 hours.
Test substance	:	61789-01-3 Fatty acids, tall-oil, epoxidized, 2-ethylhexyl esters (ETP)
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

30.05.2006 (7)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: EPIWIN (v3.02)
Year : 2002

Result : Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	4.41e-014	6.05	0
Water	3.49	900	1000
Soil	27.2	900	1000
Sediment	69.4	3.6e+003	0

Persistence Time: 2.39e+00

Test substance : SMILES =
2CCCCCC1OC1CC2OC2CCCCCCCC(=O)OC(C)COC(=O)CCCCCCCC3OC3CCCCCCC
C
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
03.10.2005 (5)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Deg. product :
Method : other: modeling
Year : 2002
GLP :
Test substance : as prescribed by 1.1 - 1.4

Result : Probability of Rapid Biodegradation (BIOWIN v4.00):
Linear Model : -0.0392
Non-Linear Model : 0.0092
Expert Survey Biodegradation Results:
Ultimate Survey Model: 2.6117 (weeks-months)
Primary Survey Model : 3.8754 (days)
Readily Biodegradable Probability (MITI Model):

Linear Model : 0.8268
Non-Linear Model : 0.2853

Test substance : SMILES = 2CCCCCC1OC1CC2OC2CCCCCCCC(=O)OC(C)COC(=O)CCCCCCCC3OC3CCCCCCC
C

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
18.05.2004 (4)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Elimination :
Method : other
Year : 2002
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Taken alone, the estimated log Kow > 6.2 indicates a high potential for bioaccumulation according the TGD. Using the non-linear QSAR recommended for substances having log Kow > 6, a log BCF value of 4.6 is estimated. However, substances having molecular weight > 700 Daltons are considered to have low bioaccumulation potential, due to steric hindrance of membrane permeation.
If taken up into fish, these fatty acid ester substances are expected to be rapidly metabolized and excreted. Due to their demonstrated potential for rapid metabolism in fish, the category of linear aliphatic fatty acid esters have recently been categorized by Environment Canada as having low potential to bioaccumulate.

Result : BCF Program (v2.15) Results:
==========
SMILES :
C(OC(=O)CCCCCCCC5OC5CC4OC4CCCCC)C(OC(=O)CCCCCCCC6OC6CCCCCCCC)(OC(=O)C

CCCCCCCCCCCCCCCC)CCCCCC1OC1CC2OC2CCCCCCCC(=O)OC(C)COC(=O)CCCCCCCC3OC3
CCCCCCCC
CHEM :
MOL FOR: C95 H170 O16
MOL WT : 1568.40

Bcfwin v2.15 ----------
Log Kow (estimated) : 31.21
Log Kow (experimental): not available from database
Log Kow used by BCF estimates: 6.20 (user entered)

Equation Used to Make BCF estimate:
Log BCF = 0.77 log Kow - 0.70 + Correction

Correction(s): Value
Alkyl chains (8+ -CH2- groups) -1.500

Estimated Log BCF = 2.574 (BCF = 375)

Reliability : (2) valid with restrictions
Modeled data

30.05.2006 (5)

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

Species	:	other: study waived - see remarks for justification
Endpoint	:	
Exposure period	:	
Unit	:	
Analytical monitoring	:	yes
Method	:	other
Year	:	2005
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Method : A chronic daphnia study using 68609-92-7 Octadecanoic acid (Z)-, epoxidized, ester w/propylene glycol (EODA) was proposed.

During the study prework to prepare a water accomodated fraction (WAF) of EODA it became apparent that phase separation could not be achieved through settling or centrifugation and it would be necessary to filter the test solutions to remove undissolved test material. Non-dissolved material present in test media has the potential to exert physical effects on test organisms which are unrelated to toxicity.

Following the OECD recommended procedures for preparation of a WAF, aqueous mixtures of the test substance were prepared in daphnid culture water at loadings of 1, 10, and 100 mg/L (three replicates per loading). The mixtures were gently stirred for seven days, then filtered through a 0.2 µm filter. Regardless of the loading concentration, all filtrates of these mixtures appeared clear, and no undissolved material was revealed using the Tyndall effect. Therefore, two replicates from each loading were analyzed for dissolved test substance using a derivatization GC-MS method.

The analytical method involved a derivitization, followed by gas chromatography with flame-ionization detection. Whereas multiple peaks are detected and summed in this assay, the exact chain length of the homologue(s) attributed to each peak was not determined. The analytical method showed suitable recovery of each peak from water samples, compared

to known spikes in organic solvent.

Remark : It is the nature of these EOD materials to aggregate in water. They do not dissolve and remain as individual molecules in solution. This was confirmed in the attempts to prepare appropriate WAFs of the test substance, which did not contain dissolved test substance at above the method detection limit of 0.05 mg/L.

The option of conducting the chronic daphnid test with another member of the EOD family was considered, however similar results are expected from the WAF preparations for these poorly soluble substances. Considerable investment was made to develop an analytical method which is capable of detecting sub-mg/L concentrations of test substance dissolved in water. Further enhancements of the method, were not expected to achieve significantly lowered detection limits.

Result : No substance-specific peak was detected in any of the chromatograms for analysis of the WAF solutions. The limit of detection was 0.05 mg/L. Recoveries for spiked water samples over the range of 0.5 mg/L to 10 mg/L were between 69% and 84%.

It appears that the true solubility of the substance in daphnia medium is below 0.05 mg/L and therefore analytical confirmation of test concentrations and test substance stability in the test medium would not be possible.

There was no water soluble test substance detected above 0.05 mg/L in a WAF prepared from a loading of 100 mg/L. The water solubility value is different than that reported elsewhere in the SIAR, SIAP, and IUCLID and is likely due to presence of undissolved (micro-emulsion) test substance remaining in the water soluble solutions.

Conclusion : There was no water soluble test substance detected above 0.05 mg/L in a WAF prepared from a loading of 100 mg/L. Therefore, considering the structure and low water solubility of the test substance, it was concluded that the WAF is not likely to exert measurable effects on daphnids, and a test would not provide meaningful, quantitative information on such effects. Further laboratory investigation of the chronic toxicity of this substance to aquatic organisms is therefore deemed not necessary.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

18.05.2006 (6)

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

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

5.5 GENETIC TOXICITY 'IN VITRO'

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

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

(1) AopWIN (v1.90) (2002)

(2) Arkema (2005) Personal Communication

(3) Atofina (2001) Material Safety Data Sheet, VIKOFLEX (R) 4964 Epoxidized Vegetable Oil. Revision: 6 27 SEP 2001

(4) BIOWIN (v4.00) and MITI Model (2002)

(5) EPIWIN (v3.05) (2002)

(6) RCC Ltd (2005)

(7) Safepharm Laboratories (2002) Determination of General Physico-chemical Properties, Project Number 1666/001

(8) SafePharm Laboratories (2002) Determination of General Physico-Chemical Properties, Project Number 1666/003

(9) SafePharm Laboratories (2002) Determination of Vapour Pressure, Project Number 1666/004

(10) World Health Organization (1967) Toxicological Evaluation Of Some Antimicrobials, Antioxidants, Emulsifiers, Stabilizers, Flour-Treatment Agents, Acids and Bases, FAO Nutrition Meetings, Report Series No. 40A,B,C, WHO/Food Add./67.29, 1967

(11) World Health Organization (1974) WHO FOOD ADDITIVES SERIES NO. 5 Toxicological evaluation of some food additives including anticaking agents, antimicrobials, antioxidants, emulsifiers and thickening agents. Geneva 1974

I U C L I D

Data Set

Existing Chemical	:	ID: 8013-07-8
CAS No.	:	8013-07-8
EINECS Name	:	Soybean oil, epoxidized
EC No.	:	232-391-0
TSCA Name	:	Soybean oil, epoxidized

Producer related part

Company	:	Epona Associates, LLC
Creation date	:	01.10.2002

Substance related part

Company	:	Epona Associates, LLC
Creation date	:	01.10.2002
Status	:	
Memo	:	EOD
Printing date	:	30.05.2006
Revision date	:	
Date of last update	:	30.05.2006
Number of pages	:	172
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

Type	:	cooperating company
Name	:	
Contact person	:	
Date	:	
Street	:	
Town	:	
Country	:	
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	

01.10.2002

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

Comment : Category Justification

Remark : This category consists of related fatty acid esters. ETP is a monoester with 2-ethylhexanol. EODA is a diester with propylene glycol. ESBO and ELSO are triesters with glycerol (triglycerides). These materials are considered a category for purposes of environmental and health hazard screening assessments because of the similarities metabolism of these materials in microbial, aquatic and mammalian systems. Uptake of any member of this category by microorganisms, aquatic species or mammals is expected to result in quite rapid metabolism by esterases. Carboxylesterases have been demonstrated to be present in many families of fish and aquatic invertebrates as well as mammals (Miller et al., 1981, Sugihara et al., 1994, Escartin and Porte, 1997 and Barron et al., 1999). The action of the esterase will result in a mixture of epoxidized fatty acids and 2-ethylhexanol from ETP, epoxidized fatty acids and propylene glycol from EODA, and epoxidized fatty acids and glycerol from ESBO and ELSO. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

In mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides.

Lipase is an enzyme that assists in the breakdown and digestion of fat in the body. Pancreatic lipase works at the oil/water interface since triglycerides are insoluble. During metabolism in the GI tract, pancreatic lipase preferentially hydrolyzes triglycerides to release the free fatty acids from the SN-1 and SN-3 (terminal) positions of the glycerol backbone. Other products of metabolism are mono- and diglycerides. The monoglycerides, diglycerides, and fatty acids can be absorbed (World Health Organization, 1974)

In a similar manner, pancreatic lipase and other digestive enzymes have been shown to hydrolyze propylene glycol monoesters and diesters in vitro. The absorption, metabolism and hydrolysis of propylene glycol distearate (which is structurally similar to EODA) were studied in rats using isotopically labelled compounds. These processes for the propylene glycol esters were found to be similar to those of the glycerol esters. So, there is evidence that the propylene glycol esters of fatty acids are hydrolyzed to propylene glycol and fatty acids. (World Health Organization, 1967)

The ETP structure is similar to that of the monoglycerides, formed from the ELSO and ESBO. Further hydrolysis can also occur via carboxylesterase activity.

Hydrolysis data for 61789-01-3 (ETP) is considered to be representative of 68609-92-7 (EODA), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Biodegradation, genetic toxicity, repeated dose, reproductive and developmental data for 61789-01-3 (ETP) and 8013-07-8 (ESBO) are considered to be representative of 68609-92-7 (EODA) and 8016-11-3 (ELSO). The chronic daphnia data for 68609-92-7 (EODA) are considered to be representative of 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Acute toxicity data for 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO), are considered to be representative of 68609-92-7 (EODA).

06.01.2006 (59) (60)

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	Soybean oil, epoxidized
Smiles Code	:	
Molecular formula	:	
Molecular weight	:	
Petrol class	:	

06.09.2005

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	= 100 % w/w

Colour : Amber (light)
Odour : Bland

24.11.2003 (2) (24) (26) (55)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Admex E LO

01.10.2002

Drapex 6.8

01.10.2002

Epocizer P 206

01.10.2002

Epoxidized soy oils

01.10.2002

Epoxidized soya oils

01.10.2002

Epoxidized Soybean Oil

06.09.2005

Epoxizer P 206

01.10.2002

Epoxol EPO

01.10.2002

Fatty acid, soybean oil, epoxidized

01.10.2002

Fatty acid, soybean oil, epoxidized:flexol epo

01.10.2002

Flexol EPO

01.10.2002

G-62

01.10.2002

Kronox S

01.10.2002

P 206 (VAN)

01.10.2002

PX-800

01.10.2002

Reoplast 39

01.10.2002

Soyabean oil, epoxidized

01.10.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 45359 - 226796 tonnes produced in 2002

22.09.2005

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : use
Category :

Remark : ESBO is approved for use as inert ingredients in pesticides
.

06.01.2006 (56)

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 : = -2.2 °C
Sublimation :
Method : OECD Guide-line 102 "Melting Point/Melting Range"
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : The pour point of the test material was determined to be 271 (-2.15 degrees C) +/- 3 K.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
19.11.2002 (49)

Value : = 6 °C
Sublimation :
Method : other
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Test substance : Trade name PX-800; composition not available
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
07.11.2002 (46)

2.2 BOILING POINT

Value : °C at 1016 hPa
Decomposition : yes
Method : OECD Guide-line 103 "Boiling Point/boiling Range"
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : As a result of the low rate of enthalpy change during decomposition, the onset of boiling temperature can only be approximated.

The test material decomposed from approximately 474 K (200.85 degrees C) at 101.60 kPa (1016.0 hPa) without boiling. As a result, no value for boiling point could be determined.

From data obtained in the vapour pressure study (SPL Project Number 1666/005), the boiling point of the test material was estimated to be >633 K at 101.325 kPa.
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.05.2004 (49)

2.3 DENSITY

Type : density
Value : = .994 - .998 g/cm³ at 20 °C
Method : other
Year : 1963
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
22.09.2005 (11) (57)

Type : density
Value : = .99 g/cm³ at 25 °C
Method : other
Year : 2005
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

06.09.2005 (22)

Type : density
Value : = .996 g/cm³ at 25 °C
Method : other
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
07.11.2002 (46)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : < .001 hPa at 25 °C
Decomposition :
Method : OECD Guide-line 104 "Vapour Pressure Curve"
Year : 2002
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Result : Vapor pressure = 8.4 x 10-8 Pa at 25 degrees C (Pa/100 = hPa)
Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
07.05.2003 (50)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : > 6.2 at °C
pH value :

Method	:	OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The standard used was DDT. The pH of the mobile phase was adjusted to 3 to assure that the test substance was tested in non-ionized form.
Result	:	Substances having a log10Pow greater than 3 are regarded as having the potential to bioaccumulate in the environment.
Conclusion	:	The partition coefficient of the test material was determined to be >1.59 x 10+6, log10Pow >6.20.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

18.05.2004 (49)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= .00099 g/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	OECD Guide-line 105
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	(2) It is the nature of these EOD materials to form an emulsion upon mixing in water. They do not dissolve and they do not remain as individual molecules in solution, which reflects the difficulty with which the undissolved microemulsion is separated from true aqueous solution. This was confirmed in the attempts to prepare appropriate water accommodated fractions (WAF) of EODA (CAS number 68609-92-7), which did not contain dissolved test substance at or above the method detection limit of 0.05 mg/L. These results from the WAF preparation suggest that actual water solubility of the EOD substances are lower than reported above.
Result	:	On completion of the equilibration period, all samples were observed to be opaque, white, turbid solutions with an oily layer on the surface. Even upon centrifugation at 10,000 rpm for 30 minutes, the sample solution remained turbid, with the degree of suspended excess undissolved test material increasing from sample 1 to 3. Therefore filtration of the samples was essential to eliminate this emulsion prior to analysis. The gel permeation chromatography (GPC) profiles obtained during analysis of the definitive test indicated that although test material was present in the sample solutions, it represented only the lower molecular weight fraction of the test material components. This was concluded since with GPC analysis, retention time is proportional to a decrease in molecular weight and the sample solution peaks observed

overlapped only the extreme lower molecular weight region of the standard solution peak profile (the test material, having been derived from a natural product, would present a range of chain lenths/molecular weights). Therefore the dissolved content present in the sample solutions poorly represented the test material composition as a whole.

The preliminary water solubility test indicated that the column elution method should have been performed, as the solubility was less than 1 x 10-2 g/l. However, due to the physical nature of the test material, it was not possible to use this method. Experience has shown that coating of liquid test
materials onto glass beads causes these beads to adhere together, forming a plug within the column which prevents water circulation.

Conclusion : The water solubility of the test material has been determined to be 1.36 x 10-3 g/l of solution at 20.0 +/- 0.5 deg C. However, from the gel permeation chromatography (GPC) profiles generated during analysis, the sample solutions contained only the lower molecular weight fraction of the test material.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
18.05.2004 (49)

Solubility in : Water
Value : = 1 other:g/100 g water at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Test substance : Trade name PX-800; composition not available
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
17.11.2005 (46)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 315 °C
Type :
Method : other
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Test substance : Trade name PX-800; composition not available
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.

07.11.2002 (46)

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

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 1.9 hour(s)
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	
Rate constant	:	= .0000000000664071 cm³/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	other (calculated): AopWIN (v1.90)
Year	:	2002
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Atmospheric Oxidation (25 deg C) [AopWin v1.90]: Hydroxyl Radicals Reaction: OVERALL OH Rate Constant = 66.4071 E-12 cm3/molecule-sec Half-Life = 0.161 Days (12-hr day; 1.5E6 OH/cm3) Half-Life = 1.933 Hrs
Test substance	:	SMILES Code = C(OC(=O)CCCCCCCC2OC2CC1OC1CCCCC)C(OC(=O)CCCCCCCC3OC3CCCCCCCC)(OC(=O)CCCCCCCCCCCCCCCCC)
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

18.05.2004 (1)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	OECD Guide-line 111 "Hydrolysis as a Function of pH"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No determination was possible by method 111 of the OECD Guidelines for Testing of Chemicals, 12 May 1981 due to the negligible solubility of the test material in water, 1.36 x 10-3 g/l of solution at 20.0 +/- 0.5 deg C. Secondly and more critically, the test material found in solution during the water solubility study represented only the lower molecular weight range of the test material components. Therefore working at half this water solubility value, the maximum concentration permitted by the method guideline, was

not applicable since the value does not address the more abundant, higher molecular weight fraction of the test material.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
19.07.2005 (49)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type : fugacity model level III
Media :
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other: EPIWIN (v3.05)
Year : 2002

Result : Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	6.45e-022	3.89	0
Water	3.49	900	1000
Soil	27.2	900	1000
Sediment	69.4	3.6e+003	0

Persistence Time: 2.39e+00

Test substance : SMILES Code =
C(OC(=O)CCCCCCCCC2OC2CC1OC1CCCCC)C(OC(=O)CCCCCCCCC3OC3CCCCCCCC
)(OC(=O)
CCCCCCCCCCCCCCCCC)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
03.10.2005 (25)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : other:bacteria collected from a sewage treatment plant
Concentration : 10 mg/l related to Test substance
20 mg/l related to Test substance

Contact time	:	28 day(s)
Degradation	:	= 79 (±) % after 28 day(s)
Result	:	readily biodegradable
Kinetic of testsubst.	:	5 day(s) = 42 % 11 day(s) = 68 % 18 day(s) = 76 % 22 day(s) = 75 % 28 day(s) = 79 %
Control substance	:	Aniline
Kinetic	:	5 day(s) = 19 % 28 day(s) = 94.4 %
Deg. product	:	
Method	:	OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year	:	1988
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Degradation: 92% degradation after 28 days at a concentration of 20 mg/L and 79% degradation after 28 days at a concentration of 10 mg/L. No explanation was offered for why a higher degradation rate was noted at the higher concentration. Both results indicate this material is readily biodegradable. Method consistent with EEC Directive 79/831 Annex V Part C 5.2
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

18.05.2004 (16)

Type	:	aerobic
Inoculum	:	domestic sewage, adapted
Contact time	:	20 day(s)
Degradation	:	= 24 (±) % after 20 day(s)
Result	:	other: not readily biodegradable
Kinetic of testsubst.	:	5 day(s) = 4 % 15 day(s) = 13 % 20 day(s) = 24 % % %
Deg. product	:	
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	"Standard methods for the examination of Water and Wastewater." 13th Edition, Amer. Pub. Health Assn., New York, N.Y. (1971) Domestic wastewater (non-acclimated and acclimated) was used as seed material to clean BOD bottles. Concentrations of 3, 7 and 10 mg/l test article were added to BOD bottles with specified minerals and buffer. At least two of the three concentrations were tested in duplicate. Dissolved oxygen (DO) was monitored periodically about five times over 20 days. When DO dropped below 4.0 mg/l the contents were re-aerated. Ammonia nitrogen and organic nitrogen were analyzed for routinely during the course of the test. Results of the biodegradation test were expressed in terms of %

bio-oxidation:

$$\% \text{ Bio-oxidized} = 100 \frac{(O'a - O'b)}{Cx * T(lambda)OD}$$

where:
O'a = cumulative oxygen uptake for the oxidation of the carbonaceous material in the test sample bottle from day zero to the day of interest, mg/l
O'b = cumulative oxygen uptake in a blank, containing the same amount and type of microbial seed as the test sample bottle, from day zero to the day of interest, mg/l
Cx = initial concentration of compound being tested, mg/l
T(lambda)OD = theoretical oxygen demand or the weight ratio of oxygen required per mg of compound for complete conversion of the compound to carbon dioxide and water. Organic nitrogen was assumed to be in the form of ammonia following oxidation of the carbonaceous portion of the material.

Remark : Inoculum was settled domestic wastewater filtered through glass wool.
The results by Price et al. (1974) are usually considered to be valid with restrictions. The test conditions are close to those in the OECD 301 series. The main uncertainty resides in the concentration of the inoculum, which was not explicitly determined. Positive results from the same study have often been used in previous assessments to confirm the ready biodegradability of the corresponding substances."

Result : Under test conditions using non-acclimated sludge, biodegradation of ESBO was 0% at 20 days. Using acclimated sludge, the biodegradation of ESBO was 24% at 20 days.

Reliability : (2) valid with restrictions
20.01.2006 (48)

Deg. product :
Method : other: modeling
Year : 2002
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : Probability of Rapid Biodegradation (BIOWIN v4.00):
Linear Model : 0.1089
Non-Linear Model : 0.0592
Expert Survey Biodegradation Results:
Ultimate Survey Model: 2.4260 (weeks-months)
Primary Survey Model : 3.9659 (days)
Readily Biodegradable Probability (MITI Model):
Linear Model : 1.1702
Non-Linear Model : 0.6625

Test substance : SMILES Code =
C(OC(=O)CCCCCCCC2OC2CC1OC1CCCCC)C(OC(=O)CCCCCCCC3OC3CCCCCCCC
)(OC(=O)
CCCCCCCCCCCCCCCCC)

Reliability : (2) valid with restrictions
18.05.2004 (3)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Elimination :
Method : other
Year : 2002
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Taken alone, the estimated log Kow > 6.2 indicates a high potential for bioaccumulation according the TGD. Using the non-linear QSAR recommended for substances having log Kow > 6, a log BCF value of 4.6 is estimated. However, substances having molecular weight > 700 Daltons are considered to have low bioaccumulation potential, due to steric hindrance of membrane permeation.
If taken up into fish, these fatty acid ester substances are expected to be rapidly metabolized and excreted. Due to their demonstrated potential for rapid metabolism in fish, the category of linear aliphatic fatty acid esters have recently been categorized by Environment Canada as having low potential to bioaccumulate.

Result : BCF Program (v2.15) Results:
==========
SMILES :
C(OC(=O)CCCCCCCC5OC5CC6OC6CC7OC7CC)C(OC(=O)CCCCCCCC
4OC4CCCCCCC)C(OC(=
O)CCCCCCCC1OC1CC2OC2CC3OC3CC)
CHEM :
MOL FOR: C56 H94 O13
MOL WT : 975.37

Bcfwin v2.15 -
Log Kow (estimated) : 12.83
Log Kow (experimental): not available from database
Log Kow used by BCF estimates: 6.20 (user entered)

Equation Used to Make BCF estimate:
Log BCF = 0.77 log Kow - 0.70 + Correction

Correction(s): Value
Alkyl chains (8+ -CH2- groups) -1.500

Estimated Log BCF = 2.574 (BCF = 375)

Reliability : (2) valid with restrictions
Modeled data

30.05.2006 (25)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC0	:	= 580 calculated
LC50	:	= 900 calculated
LC100	:	> 1000 calculated
Limit test	:	
Analytical monitoring	:	no
Method	:	other
Year	:	1988
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	DIN-Vorschrift 38412-L15 Values are based on nominal concentrations. Tests were conducted in 20-liter aquaria filled with 15 liters using dechlorinated tap water (carbon filter) with 10 fish per exposure at concentrations of 100, 180, 320, 580 and 1000 mg/l. No stock solution was prepared. The test substance was added directly to the water in the tanks to produce the desired concentration. Initially the test substance appeared to be homogeneously distributed in all test concentrations but a slight deposit was observed with concentrations 100-1000 mg/l after 48 hours. The following water parameters were noted: Adjusted hardness - 267 mg CaCO3/l, 14.9 degrees d, and Mol Ca/Mg was approximately 4/1; Temperature - 20 +/- 1C; Aeration - gently aeration during the test; Lighting - fluorescent light for 16 hours daily. Oxygen, pH and temperature were measured daily. Two control groups were included, one exposed to the reconstituted water only and a vehicle control (1000 mg DMF per liter water). The following parameters were noted for the fish: Length - 65 mm; Weight 1.90 g; Loading - 1.27 g/l; Index of condition - K: 0.7 mg/l; Feeding - None during testing; Acclimation period - 35 days.
Remark	:	Based on a known water solubility of 0.99 mg/L, the reported nominal concentrations for this test material are questionable. Whereas the duration of the acute study with fish (48 h) was shorter than specified in current OECD guidelines (96 h), it should also be considered that the concentrations tested were well above the limit of solubility. These test conditions may be considered to represent a worst-case exposure condition, as the possibility for both direct toxicity (narcosis) of dissolved substance and solvent vehicle, and indirect toxicity (physical effects) of undissolved test substance were represented. Regardless of this potential for multiple modes of toxicity, acute LC50 value indicates the substance to be practically non-toxic to fish on an acute basis.
Result	:	Seven of ten fish exposed to 1000 mg/l died by 48 hours. No other deaths were noted during testing. A slight effect on swimming behavior was noted at 180, 320, 580, and 1000 mg/l

at 24 and 48 hours (no additional details provided), and a slight loss of equilibrium and respiratory function wer

Reliability : (4) not assignable
18.05.2006 (15)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC0	:	> 100 calculated
EC50	:	> 100 calculated
EC100	:	> 100 calculated
Analytical monitoring	:	no
Method	:	OECD Guide-line 202
Year	:	1988
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : The test material is insoluble in water. A stock solution was prepared: 4.0 g of test material were dissolved in and made up to 10 ml with DMF. This solution was diluted to 100 mg/l with water.

Test concentrations were 10, 18, 32, 58 and 100 mg/l.

Nominal: The calculated amounts of stock solution to produce the desired test concentrations were given into the water and were homogeneously distributed. The daphnia were then transferred into the beakers.

Small parts of the test substance were swimming at the surface of the test solutions at concentrations 10-100 mg/l (nominal) from the start of the test.

Remark : Based on a known water solubility of 0.99 mg/L, the reported nominal concentrations for this test material are questionable.

Whereas the duration of the acute study with crustaceans (24 h) was shorter than specified in current OECD guidelines (48 h), it should also be considered that the concentrations tested were well above the limit of solubility. These test conditions may be considered to represent a worst-case exposure condition, as the possibility for both direct toxicity (narcosis) of dissolved substance and solvent vehicle, and indirect toxicity (physical effects) of undissolved test substance were represented. Regardless of this potential for multiple modes of toxicity, acute EC50 value indicates the substance to be practically non-toxic to crustacea on an acute basis.

Result : No immobilization was noted in any treated organism.
Reliability : (4) not assignable
18.05.2006 (17)

Type	:	static
Species	:	Artemia salina (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l

TL50	:	= 240
Analytical monitoring	:	no
Method	:	other
Year	:	1974
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Adaptation of method presented by Tarzwell, C.M., "Standard methods for Determination of Relative Toxicity of Oil Dispersants and Various Oils to Aquatic Organisms." Proc. Joint Conf. on Prevention and Control of Oil Spills, sponsored by API and EPA (December 15-17, 1969) Toxicity screening test: 30-50 newly hatched shrimp/ml (<48 hours old) were exposed to a 1% solution of the test article at concentrations of 100, 1000 and 10,000 mg/l in a total volume of 100 ml seawater. The bottles were loosely capped and incubated at ambient temperature for 24 hours. At the end of the exposure period the number of live and dead shrimp were counted.
Remark	:	TL=Tolerance limit; TL50 = LC50 Based on a known water solubility of 0.99 mg/L, the reported nominal concentrations for this test material are questionable. Whereas the duration of this acute study with crustaceans (24 h) was shorter than specified in current OECD guidelines (48 h), it should also be considered that the concentrations tested were well above the limit of solubility. These test conditions may be considered to represent a worst-case exposure condition, as the possibility for both direct toxicity (narcosis) of dissolved substance, and indirect toxicity (physical effects) of undissolved test substance were represented. Regardless of this potential for multiple modes of toxicity, acute LC50 value indicates the substance to be practically non-toxic to crustacea on an acute basis.
Reliability	:	(4) not assignable

18.05.2006 (5) (48)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	growth rate
Exposure period	:	72 hour(s)
Unit	:	mg/l
NOEC	:	= .7 calculated
EC50	:	= 8 calculated
Limit test	:	
Analytical monitoring	:	yes
Method	:	Directive 87/302/EEC, part C, p. 89 "Algal inhibition test"
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Stock solution: 100.4 mg test substance and 2 ml 0.1% alkylphenopolyglycolether (ARKOPAL) in dist water were mixed and made up to 1000 ml with water.

Test concentrations:
Nominal: 1.23, 3.7, 11, 33, and 100 mg test substance/l
Actual initial: 0.7, 2.3, 6.8, 24.0, and 81.0 mg test substance/l

Controls:
Blank: water
Vehicle: 2.0 mg alkylphenolpolyglycolether (ARKOPAL)/l

Replicates: Each test concentration was tested in 3 replicates, the blank control in 6.

Remarks: Calculated amounts of the stock solution to produce the desired test concentrations were given into the water and were homogeneously distributed. The algae were then transferred into the flasks. The test substance was homogeneously distributed in the test vessels at all test times and test concentrations.

Sampling for analysis: Composite samples of each test concentration were drawn by mixing identical volumes of the test solutions taken from the approximate center of the test vessels. They were taken immediately before exposure and after 72 hours exposure and kept at -18 C to -22 C until analysis.

Cell densities were measured at 24, 48 and 72 hours exposure on a "TOA" cell counter. Temperature was continuously measured and maintained at 23 +/- 1 C. pH was measured at 0h and 72h exposure.

The EbC-50 values were calculated according to the maximum likelihood method, logit model.

Remark : Analytical monitoring used VIS spectroscopy. Due to unknown reasons no test substance was found at the end of the exposure at low test concentrations. Therefore, values are based on actual initial concentrations.

A re-evaluation of the acute algal report finds this to be a well-documented study, which was conducted according to the EEC test guideline and in compliance with GLP. An independent statistical analysis of the cell density data confirmed that the reported EbC50 value (8.0 mg/L) has correctly accounted for inhibition by the test vehicle (alkylphenolpolyglycolether). Whereas poor recovery of test substance was observed after 72 h (by UV/VIS spectroscopy), this could be attributed to test substance falling out of solution following its initial dissolution via the solvent vehicle (DMF).

Reliability : (2) valid with restrictions
A re-evaluation of the acute algal report finds this to be a well-documented study, which was conducted according to the EEC test guideline and in compliance with GLP.

18.05.2006 (18)

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	:	> 5000 mg/kg bw
Species	:	rat
Strain	:	other
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other
Doses	:	5000 mg/kg bw
Method	:	other
Year	:	1981
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A single dose of 5 grams was administered.
Remark	:	Strain:Tif:RAIf (SPF) Vehicle: PAG
Result	:	Animals exhibited breathing difficulty and diarrhea for several hours. Animals had a "hunched" appearance and "ruffled fur" lasting for 1-4 days. Examination of an undisclosed range of organs revealed no gross abnormalities.
Test substance	:	Reoplast 39 is 100% Epoxidized Soybean Oil
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

05.08.2005 (5) (6) (13)

Type	:	LD50
Value	:	= 22.5 ml/kg bw
Species	:	rat
Strain	:	other: Carworth-Wistar
Sex	:	male
Number of animals	:	19
Vehicle	:	
Doses	:	
Method	:	other: generally follows OECD 401
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 Carworth-Wistar, non-fasted male rats, 5 to 6 weeks of age and 90-120 grams in weight were dosed with 7.95, 15.8, 31.6 or 63 ml/kg (high dose consisted of 4 rats). The test article was undiluted. Rats were maintained for 14 days after dosing for determining lethality. Any animals that died were necropsied. Thompson's method of calculating the median-effective dose (LD50) was applied to the 14-day mortality data.
Result	:	Lethality was observed at 15.8, 31.6 and 63.0 ml/kg. All animals fed 63.0 ml/kg died on day 1. Three of 5 rats dosed with 31.6 ml/kg died on day 1. Two of 5 rats dosed with 15.8 ml/kg died, one on day 1 and one on day 6. There were no marked symptoms of distress noted in animals dosed with 63.0 ml/kg. At 31.6 and 15.8 ml/kg, the rats

that died had congested lungs, mottled livers, pale kidneys with congested interiors and considerable intestinal irritation.

No further information provided.

Source : The Dow Chemical Company Midland, Michigan
Test substance : Soybean Oil Epoxide (EP-302)
Reliability : (2) valid with restrictions
07.05.2003 (5) (6) (41) (57)

Type : LD50
Value : = 41.5 ml/kg bw
Species : rat
Strain : other:Harlan-Wistar
Sex : female
Number of animals :
Vehicle : no data
Doses :
Method : other
Year : 1976
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Compounds were administered by gavage to 90- to 120-gram Harlan-Wistar rats. The rats were nonfasted and were dosed the day they were weighed. There were five dose levels used in this study. LD50 was calculated by the moving average method based upon a 14-day observation period.
Remark : The report does not indicate the the number of animals or the dose levels used. Dose levels differed by a factor of 2 in geometric series. Based on other reports from the same time period, 5 animals/dose were used.
Test substance : FLEXOL (TM); soybean oil epoxide; 519-3; 41376; 4172; TF. 100% Epoxidized soybean oil.
Reliability : (2) valid with restrictions
05.08.2005 (7)

Type : LD50
Value : = 40000 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses :
Method : other
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Test substance : Trade name PX-800; composition not available
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
18.05.2004 (6) (46)

Type : other
Value :
Species : rat
Strain : no data

Sex	:	no data
Number of animals	:	10
Vehicle	:	no data
Doses	:	
Method	:	other:unknown
Year	:	1973
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A single dose of 5 ml/kg bw to ten rats caused slight breathing difficulty, lethargy and diarrhea for several hours. Examination of undisclosed ranges of tissues and organs revealed no gross abnormalities.
Test substance	:	Reoplast 39 is 100% Epoxidized Soybean Oil
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

18.05.2004 (6) (12) (33)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	6
Vehicle	:	
Doses	:	
Exposure time	:	
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A mist was generated at 170C by passing air at 2.5 liters/minute through fritted glass disc immersed in 50 ml of the compound. Groups of 6 adult male rats were exposed for either 30 or 60 minutes and survivors were held for observation for a total of 14 days.
Remark	:	The color change observed within 10 minutes is very likely due to test material degradation. The expected degradation products and the approximate concentration of the saturated vapor are not known. This information is not necessary as this study does not fulfill a critical SIDS endpoint.
Result	:	Within 10 minutes after the compound reached a temperature of 170C, the color changed from amber to light yellow. All animals exposed for 30 minutes survived. All animals exposed for 60 minutes died. Lung hemorrhage was the immediate cause of death in the 1-hour exposure group. The mist caused irritation of the skin, gaspy breathing and muscular incoordination (ataxia). No further information provided.
Source	:	The Dow Chemical Company Midland, Michigan
Test substance	:	100 % Soybean Oil Epoxide (EP-302)

Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meet important criteria of today's standard methods.

24.11.2003 (41)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 20 ml/kg bw
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	4
Vehicle	:	
Doses	:	
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of four male albino New Zealand strain rabbits, 3 to 5 months of age and averaging 2.5 kg were immobilized during the 24-hour skin contact period with 20 ml/kg bw EP-302. The material remained in place during the 24-hour contact period with "Vinylite" sheeting. After the 24-hour period the sheeting was removed and the animals were caged for the remainder of the 14-day observation period. Thompson's method for calculating the LD50 was used.
Result	:	A dosage of 20 ml/kg of the undiluted compound resulted in survival of all four rabbits. No particular damage other than transient erythema resulted. The LC50 is >20 ml/kg.
Source	:	The Dow Chemical Company Midland, Michigan
Test substance	:	100% Soybean Oil Epoxide (EP-302)
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

24.11.2003 (5) (6) (41) (57)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	other
Value	:	
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	1968
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	0.5 ml ESBO injected i.p. Dose approximately 25 g/kg bw.
Result	:	No overt signs of toxicity

Test substance	:	ESBO
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.
18.05.2004		(6) (27)

Type	:	other
Value	:	
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	
Route of admin.	:	other:intradermal
Exposure time	:	
Method	:	other
Year	:	1968
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Result	:	Intradermal injection of neat ESBO did not cause irritation.
Test substance	:	neat ESBO
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.
18.05.2004		(6) (27)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Open
Exposure time	:	24 hour(s)
Number of animals	:	5
Vehicle	:	
PDII	:	
Result	:	slightly irritating
Classification	:	
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Five rabbits received 0.01 ml undiluted test material to the uncovered, clipped skin of the belly.
Remark	:	Under the more severe conditions of the dermal toxicity study (20 ml applied for a 24-hour contact period) conducted in four rabbits, no particular damage other than transient erythema resulted.
Result	:	One of five rabbits had minimal capillary injection of the skin. The remaining four rabbits exhibited no response. No additional information provided.
Source	:	The Dow Chemical Company Midland, Michigan
Test substance	:	100% Soybean Oil Epoxide (EP-302)
Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meet important criteria of today's standard methods (only 0.01 ml was used).

19.07.2005 (5) (6) (41) (57)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Open
Exposure time	:	24 hour(s)
Number of animals	:	5
Vehicle	:	
PDII	:	
Result	:	slightly irritating
Classification	:	
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of 5 rabbits were dosed three times daily at three-hour intervals with 0.01 ml undiluted to the uncovered, clipped skin of the belly.
Result	:	The test material did not produce an increase in skin irritation. The daily readings were scored as 4, 3 3 (total) with no response greater than capillary injection on any of the five rabbits.
Source	:	The Dow Chemical Company Midland, Michigan
Test substance	:	100% Soybean Oil Epoxide (EP-302)
Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meet important criteria of today's standard methods (only 0.01 ml was used).

19.07.2005 (41)

Species	:	rabbit
Concentration	:	
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	moderately irritating
Classification	:	
Method	:	other
Year	:	1981
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Covered contact for 24 hours
Result	:	Treatment caused mild reddening and minimal swelling of intact skin and was moderately irritating to abraded skin.
Test substance	:	Commercial grade TK 11278 (Reoplast 39) is 100% Epoxidized Soybean Oil
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

18.05.2004 (5) (6) (8)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	100 %

Dose	:	.5 ml
Exposure time	:	
Comment	:	
Number of animals	:	5
Vehicle	:	
Result	:	not irritating
Classification	:	
Method	:	other:essentially follows OECD 405
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	An excess (0.5 ml) of undiluted EP-302 was instilled into the conjunctival sac of five rabbit eyes.
Result	:	There was no damage to the cornea observed.
Test substance	:	100% Soybean Oil Epoxide (EP-302)
Reliability	:	(2) valid with restrictions

24.11.2003 (5) (6) (41) (57)

Species	:	rabbit
Concentration	:	
Dose	:	.1 ml
Exposure time	:	
Comment	:	no data
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	other:unknown
Year	:	1981
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	0.1 ml of Reoplast 39 caused reddening of the conjunctiva
Test substance	:	Reoplast 39 is 100% Epoxidized Soybean Oil
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

18.05.2004 (5) (6) (9)

5.3 SENSITIZATION

Type	:	other: sensitization test
Species	:	guinea pig
Number of animals	:	20
Vehicle	:	
Result	:	not sensitizing
Classification	:	
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of twenty male albino guinea pigs were subjected to 8 intracutaneous injections (three per week on alternate days) and topical applications of a 0.1% solution during 2 1/2 weeks, followed by a 3-week incubation period prior to the challenge dose. Examination for possible sensitization

reactions was made 24 and 48 hours thereafter.

No further information provided.

Remark : This is similar to the Guinea Pig Maximization test except that an adjuvant was not used.
Result : Test material was negative in the guinea pig sensitization test.
Source : The Dow Chemical Company Midland, Michigan
Test substance : 100% Soybean Oil Epoxide (EP-302)
Reliability : (2) valid with restrictions
24.11.2003 (5) (6) (41) (57)

Type : other
Species : guinea pig
Concentration : 1st: Induction .1 % intracutaneous
2nd: Challenge .1 % intracutaneous
3rd: Challenge 30 % occlusive epicutaneous
Number of animals : 20
Vehicle : other:1:1propylene glycol:saline
Result : not sensitizing
Classification :
Method : other
Year : 1981
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Ten intracutaneous injections of 0.1 ml were given on alternate days in the induction phase. Animals were first challenged three weeks later by an injection of the same 0.1% solution, and again two weeks later with a 24-hour covered patch test using a 30% solution.
Test substance : Reoplast 39 is 100% Epoxidized Soybean Oil
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
18.05.2004 (5) (6) (10)

Type : other:workplace exposure
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method : other:workplace exposure
Year : 1980
GLP : no
Test substance : other TS:heated polyvinyl chloride film containing ESBO

Remark : Asthma developed in a worker exposed to vapor from heated polyvinyl chloride film containing ESBO. Challenge with ESBO vapor (unspecified concentration) produced asthmatic symptoms within 5 minutes.
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
18.05.2004 (5) (6) (47)

5.4 REPEATED DOSE TOXICITY

Type	:	Chronic
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	2 years
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	0, 0.1, 0.5, 1.0, 2.5 or 5% (up to approximately 1.25 g/kg bw/day)
Control group	:	yes, concurrent no treatment
LOAEL	:	= 1 %
Method	:	other
Year	:	1960
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Groups of rats (15/sex) were given diets containing up to 5% ESBO for up to 2 years. Five rats/sex/group were sacrificed at 6 months. Organ to body weight measurements were made for liver, kidney and testes. Blood studies (hemoglobin, red blood cell and differential white cell counts) were made during the eleventh and twenty-fourth months. Histopathology of heart, lung, kidney, spleen, gastroenteric, thyroid, adrenal, pancreas, gonad, muscle and bone marrow tissues was conducted on survivors from the 0, 2.5% and 5% diet groups.

Remark : Specifications for Paraplex G62 composition:

	Typical Spec limits	Spec limits
Acid Value mg KOH/g	0.3	0 - 1.0
Iodine Value	10	6 - 14
Oxirane Oxygen	6.5	6.3 - (max not given)

The conversion from % in diet to dosage as an approximate mg/kg bw/day is:

% in diet	approximate mg/kg bw/day
0	0
.1	25
.5	125
1	250
2.5	625
5	1250

Result : Growth appeared to be essentially normal at 2.5%, but appeared to be permanently low in the 5% group. A limited evaluation of the blood (red blood cell and white blood cell counts) revealed no effects. Liver weight was increased in both sexes at 1% and above. There was some evidence that kidney weight was increased in the females at 1% and above. Microscopic examination of the major tissues revealed no cellular changes at 2.5% or 5% (only dose groups examined).

The uterus was not examined.

Test substance	:	Paraplex G-62 is 100% epoxidized soybean oil
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

19.07.2005 (5) (6) (37) (54)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	15 weeks
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	Up to 5% (up to approximately 1.25 g/kg bw/day)
Control group	:	no data specified
LOAEL	:	> 1.5 %
Method	:	other
Year	:	1960
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Rats were given diets containing up to 5% ESBO for 15 weeks.
Remark	:	The conversion from % in diet to dosage as an approximate mg/kg bw/day is: % in diet approximate mg/kg bw/day 1.5 375 5 1250
Result	:	Temporary slowed growth and liver and kidney enlargement at concentrations greater than 1.5%. Liver changes (fatty infiltration) observed at 2.5% (approximately 1.3 g/kg bw/day) or greater.
Test substance	:	ESBO (iodine number 7-8 and oxygen oxirane value of 6.3-6.4)
Reliability	:	(2) valid with restrictions

19.07.2005 (5) (6) (36)

Type	:	Sub-chronic
Species	:	dog
Sex	:	no data
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	1 year
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	0.1, 1.0, 5% (up to approximately 1.25 g/kg bw/day)
Control group	:	no data specified
LOAEL	:	= 5 %
Method	:	other
Year	:	1960
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Groups of three dogs were fed up to 5% Paraplex G-60 or G-62 once per day for one year. The dogs were weighed weekly and food intake was monitored. Hematologic studies were made at study initiation, at 6 months and at 12 months. Major tissues were examined microscopically. The dogs were sacrificed at 12 months.
Remark	:	Specifications for Paraplex G62 and G60 composition:

		Typical Spec limits Spec limits G62 Spec limits G60 Acid Value mg KOH/g 0.3 0 - 1.0 0-0.5 Iodine Value 10 6 - 14 0-1.1 Oxirane Oxygen 6.5 6.3 (max not given) 6.8 (max not given) The conversion from % in diet to dosage as an approximate mg/kg bw/day is: % in diet approximate mg/kg bw/day 0 0 .1 25 1 250 5 1250
Result	:	Dogs fed 5% Paraplex G-60 or G-62 lost weight. Survival and blood parameters (hemoglobin, red and white blood cell counts) were normal in all treated groups. The major tissues were microscopically normal except for fatty liver changes (fatty infiltration) in one dog given 5% Paraplex G-62. Food intake and body weight were decreased at 5% of either grade.
Test substance	:	Paraplex G-60 or Paraplex G-62 are 100 % epoxidized soybean oil
Reliability	:	(2) valid with restrictions
19.07.2005		(5) (6) (37) (53) (54)
Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	other:albino
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	no data
Post exposure period	:	
Doses	:	0.04, 0.2, 1.0 or 5.0% (5% is approximately 1.25 g/kg bw/day)
Control group	:	yes
NOAEL	:	= .2 %
LOAEL	:	= 1 %
Method	:	other
Year	:	1971
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Specifications for Paraplex G62 composition: Typical Spec limits Spec limits Acid Value mg KOH/g 0.3 0 - 1.0

Iodine Value 10 6 - 14

Oxirane Oxygen 6.5 6.3 - (max not given)
Study conducted in 1960 and originally reported in CHF report 23-41; also reported in CHF report 34-29, issued May 17, 1971. Groups of 10 male and 10 female rats were included.
The conversion from % in diet to dosage as an approximate mg/kg bw/day is:

% in diet	approximate mg/kg bw/day
0.04	10
0.2	50
1	250
5	1250

Result : No effect on body weight gain for treated female rats. Males receiving 5% Plasticizer EPO or Paraplex G-62 had lower body weight gains than controls for the first few weeks of dosing only. Males given 5% Plasticizer EPO ate less diet than the controls. This was the only difference for the male animals given Plasticizer EPO vs. Paraplex G-62. Female animals ate less diet when given either test article at 1% or 5%. Liver weights were increased in rats fed either test article at 5% in diet; this increase was also observed in male rats fed either test article at 1%. There were no test article-related deaths. Gross findings indicated a test article-related effect of Plasticizer EPO on liver and kidney at 1% and 5%. A gross effect on the kidney (male rats at 1% or 5%) and liver (male and female rats at 5%) was observed with Paraplex G-62. Minimum effect dosage level = 1%; Maximum no ill effect dosage level = 0.2%

Test substance : Plasticizer EPO = 100% Epoxidized soybean oil; Paraplex G-62 is 100% epoxidized soybean oil

Reliability : (2) valid with restrictions

19.07.2005 (7) (39) (54)

Type : Chronic
Species : rat
Sex : male/female
Strain : no data
Route of admin. : oral feed
Exposure period : Up to 2 years
Frequency of treatm. : Daily
Post exposure period :
Doses : 0.025, .25 or 2.5% (up to 1.4 g/kg bw/d)
Control group : no data specified
NOAEL : = .25 %
LOAEL : = 2.5 %
Method : other
Year : 1986
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 48 male and 48 female rats were given diets containing up to 2.5% ESBO for up to 2 years.

Remark : The conversion from % in diet to dosage as an approximate mg/kg bw/day is:

% in diet	approximate g/kg bw/day

.025 0.014 (females)
0.01 (males)
.25 0.140 (females)
0.1 (males)
2.5 1.4 (females)
1 (males)

Result : There were no changes in survival or blood parameters. Gross and microscopic examination of organs revealed a slight change in the uterus at 2.5% (approximately 1.4 g/kg bw/day), but at 0.25% (about 140 mg/kg bw/day) and below no treatment-related effects were seen in females. In males, there were no effects up to 2.5% (about 1 g/kg bw/day).
Test substance : ESBO [iodine number 7-8, oxirane oxygen 6.3-6.4]
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.

19.07.2005 (4) (5) (6)

Type : Sub-chronic
Species : rat
Sex : no data
Strain : no data
Route of admin. : oral feed
Exposure period : up to 10 weeks
Frequency of treatm. : daily
Post exposure period : no data
Doses : 20% (approximately 10 g/kg bw/day)
Control group : yes
LOAEL : = 20 %
Method : other
Year : 1963
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Study used ESBO grades that do not use the specification of those in commerce today.
The conversion from % in diet to dosage as an approximate mg/kg bw/day is:

% in diet approximate mg/kg bw/day
20 10,000

Result : All treated groups grew more slowly than control animals fed 20% soya bean oil. Deaths occurred in groups fed ESBO with epoxide numbers equal to or greater than 49.7. Water consumption increased with epoxide number, while food intake and protein utilization decreased. Severe degeneration of the testes occurred in animals fed ESBO with epoxide numbers 105 and 111.5. Fatty degeneration of the liver and kidney was found in controls and treated groups fed ESBO of epoxide numbers 14.6-49.7. Microscopic examination of the heart and intestines (the only organs examined) revealed no treatment related effect.
Test substance : ESBO (iodine number from 14.6 - 111.5)
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.

19.07.2005 (5) (6) (34)

Type : Sub-acute
Species : rat

Sex	:	no data
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	8 weeks
Frequency of treatm.	:	daily
Post exposure period	:	no data
Doses	:	1 or 5% (1% is approximately 0.5 g/kg bw/day)
Control group	:	no data specified
LOAEL	:	= 1 %
Method	:	other
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	1% or 5% ESBO in the diet, made up to 20% of the diet with untreated soya bean oil. The conversion from % in diet to dosage as an approximate mg/kg bw/day is: % in diet approximate mg/kg bw/day 1 500 5 2500
Result	:	Retarded growth observed in animals given 1% ESBO in the diet. 6/54 animals given 5% ESBO in the diet died.
Test substance	:	ESBO (epoxide number 220)
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

19.07.2005 (5) (6) (34)

Type	:	Sub-acute
Species	:	rat
Sex	:	no data
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	12 days
Frequency of treatm.	:	daily
Post exposure period	:	
Doses	:	5% (approximately 2.5 g/kg bw/day)
Control group	:	yes
LOAEL	:	= 5 %
Method	:	other
Year	:	1988
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Six rats were used in this study.
Remark	:	The conversion from % in diet to dosage as an approximate mg/kg bw/day is: % in diet approximate mg/kg bw/day 5 2500
Result	:	Decreased growth compared with controls given soya bean oil. Liver weight and serum transaminase levels were unaffected by ESBO treatment. Biosynthesis of epoxide hydratase was increased by ESBO treatment.
Test substance	:	ESBO (oxirane oxygen 6-6.8%, iodine number unspecified)
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

19.07.2005 (6) (45)

Type	:	Sub-chronic
Species	:	rat
Sex	:	no data
Strain	:	no data
Route of admin.	:	oral unspecified
Exposure period	:	16 months
Frequency of treatm.	:	twice-weekly
Post exposure period	:	
Doses	:	1.4 g/kg bw
Control group	:	no data specified
NOAEL	:	= 1400 mg/kg bw
Method	:	other
Year	:	1961
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Result	:	No adverse effects associated with treatment
Test substance	:	Standard grade of ESBO (Plastol 10)
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

19.07.2005 (5) (6) (35) (38)

Type	:	Sub-chronic
Species	:	dog
Sex	:	no data
Strain	:	no data
Route of admin.	:	oral unspecified
Exposure period	:	12 months
Frequency of treatm.	:	twice-weekly
Post exposure period	:	no data
Doses	:	1.4 g/kg bw
Control group	:	no data specified
NOAEL	:	= 1400 mg/kg bw
Method	:	other
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Result	:	No adverse effects associated with treatment
Test substance	:	Standard grade of ESBO (Plastol 10); composition not available
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

19.07.2005 (5) (6) (35) (38)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	TA98, TA100, TA1535, TA1537 and TA102
Test concentration	:	8, 40, 200, 1000 and 5000 ug/plate (Experiment 1); 312.5, 625, 1250, 2500 and 5000 ug/plate (Experiment 2)
Cycotoxic concentr.	:	200 ug/plate (TA102 only)
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471

Year : 1992
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Toxicity range-finder experiment: Epoxidised Soybean Oil was tested for toxicity in strain TA100. Triplicate plates without and with S-9 mix were used. Negative (solvent) and positive controls were included in quintuplicate and triplicate, respectively, without and with S-9 mix.

Mutation experiments: Epoxidised Soybean oil was tested for mutation in 5 strains of Salmonella typhimurium (TA98,TA100, TA1535, TA1537 and TA102) using triplicate plates without and with S-9. Negative (solvent) controls were included in both assays, in quintuplicate without and with S-9. The mammalian liver post-mitochondrial fraction (S-9) used for metabolic activation was prepared from male Sprague Dawley rats induced with Aroclor 1254. In each experiment, bacterial strains were treated with diagnostic mutagens in triplicate in the absence of S-9. The activity of the S-9 mix used in each experiment was confirmed by AAN treatments (again in triplicate) of at least 1 strain in the presence of S-9. Because the results of the first experiment were negative, treatments in the presence of S-9 in Experiment 2 included a pre-incubation step, where the quantities of test chemical or control solution, bacteria and S-9 mix were mixed together and incubated for 1 hour at 37°C, before the addition of 2.5 ml molten agar at 46°C. Plating of these treatments then proceeded as for the normal plate-incorporation procedure. In this way, it was hoped to increase the range of mutagenic chemicals that could be detected in the assay. It should be noted that Experiment 2 TA100 solvent control treatments in the presence of S-9, resulted in counts which fell outside the historical control range. These treatments were therefore repeated, and the results reported here are from the repeat experiment.

Treatment of data
Individual plate counts from both experiments were recorded separately and the mean and standard deviation of the plate counts for each treatment were determined. The m-statistic was first calculated to check that the data were Poisson-distributed, and then Dunnett's test was used to compare the counts of each dose with the control.

Acceptance criteria: The assay was considered valid if the following criteria were met: i) the mean negative control counts fell within the normal range, ii) the positive control chemicals induced clear increases in revertant numbers confirming discrimination between different strains, and an active S-9 preparation, iii) no more than 5% of the plates were lost through contamination or some other unforeseen event.

Evaluation criteria
A test compound was considered to be mutagenic if: i) the assay was valid, ii) Dunnett's test gave a significant response ($p < 0.01$),and the data set showed a significant dose-correlation, iii) the positive responses described in (ii) were reproducible.

Toxicity
Only treatments of strain TA102 in Experiment 2 (+ S-9 only) showed signs of toxicity (as indicated by thinning of the background bacterial lawn) in this study. In this case, toxic effects were seen mostly at the 3 highest doses. It would appear that the use of a pre-incubation step particularly enhanced the toxicity of the test agent to this test strain.

Range-finder and Experiment 1 treatments were carried out using final concentrations of Epoxidised Soybean oil at 8,40, 200, 1000 and 5000 ug/plate. Precipitation, in the form of oil droplets, was observed at concentrations of 1000 and 5000 ug/plate. For Experiment 2, testing was again carried out up to a maximum concentration of 5000 ug/plate (despite the observation of precipitation), as it was possible that the compound formed an emulsion within the test system, and it was felt important to maximise the exposure of the cells to this. A narrowed dose range was also used in this experiment (312.5-5000 ug/plate) in order to examine those doses most likely to exhibit a mutagenic response. Oil droplets were observed on test plates in this experiment, following treatments of 1250 ug/plate and above.

Result : Summary:

Epoxidised Soybean oil was assayed for mutation in 5 histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of Salmonella typhimurium, both in the absence and presence of metabolic activation by an Aroclor 1254 induced rat liver post-mitochondrial fraction (S-9), in 2 separate experiments.

An initial toxicity range-finder experiment was carried out in TA100 only, using final concentrations of Epoxidised Soybean oil at 8, 40, 200, 1000 and 5000 ug/plate plus a solvent and positive control. These treatments were nontoxic, and the same dose range was retained for Experiment 1. For Experiment 2 treatments, the dose range was narrowed (312.5-5000 ug/plate) in order to investigate those concentrations most likely to exhibit a mutagenic response. In addition, a pre-incubation step was used for treatments in the presence of S-9, to increase the range of mutagens that might be detected using the assay. Precipitation (in the form of oil droplets) was observed following treatments at concentrations of 1250, 2500 and 5000 ug/plate in this experiment. Toxic effects (as indicated by a thinning of the background bacterial lawn) were also noted in this experiment, in strain TA102 in the presence of S-9, apparently enhanced by the use of a pre-incubation step. Negative (solvent) and positive control treatments were included for all strains in both experiments. The mean numbers of revertant colonies on negative control plates all fell within acceptable ranges, and were significantly elevated by positive control treatments. No Epoxidised Soybean Oil treatment of any of the tester strains, either in the absence or presence of S-9, resulted in an increase in revertant numbers sufficient to be considered as evidence of mutagenic activity. It is concluded that Epoxidised Soybean oil failed to induce

mutation in 5 strains of Salmonella typhimurium, when tested up to a maximum concentration of 5000 ug/plate, in the absence and presence of a rat liver metabolic activation system.

Test substance : Reoplast 39 (oxirane oxygen 6.4%, iodine value 4.3) is 100% Epoxidized Soybean Oil

Conclusion : No treatment with Epoxidised Soybean Oil of any of the tester strains, either in the absence or presence of S-9, resulted in a significant increase in revertant numbers. The data obtained therefore gave no indication of an ability of the test agent to induce mutation.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

01.12.2003 (6) (29)

Type : Salmonella typhimurium reverse mutation assay
System of testing : TA98 and TA100
Test concentration : 0.03, 0.09, 0.3, 0.9 and 3 mg/plate
Cycotoxic concentr. : >3 mg/plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1986
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Ames et al. 1975
The S9 mix was from livers of Aroclor 1254-induced male Sprague-Dawley rats.

Reliability : (2) valid with restrictions

29.10.2002 (42)

Type : Salmonella typhimurium reverse mutation assay
System of testing : TA98 and TA100
Test concentration : Supernatant solutions of the stomach and small intestines
Cycotoxic concentr. : At levels of 0.5 ml/plate for both organ homogenates and 0.15 ml/plate for small intestine homogenates, thick background lawns, uneven colony distribution, and reduced numbers of revertants were frequently observed.
Metabolic activation : with and without
Result : negative
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Ames et al., 1975. Stomach and small intestine tissues were removed from pairs of fasted male Long-Evans rats sacrificed at 1 and 6 hours after oral administration of epoxidized soybean oil (ESO) at 1 g/kg. Additional pairs of animals treated with distilled water at 1 g/kg served as controls. Pairs of organs were frozen, homogenized, centrifuged at 2,000 x g for 20 minutes, and filtered to prepare supernatant solutions for testing in the Ames/Salmonella plate incorporation assays in the presence and absence of an Arochlor 1254 induced mammalian (rat) metabolic activation system.

Result : When the number of TA98 and TA100 revertants/plate for homogenates prepared from rats treated with distilled water were compared to those of rats treated with ESO, no significant differences were noted. It should be noted that

the presence of endogenous histidine in the supernatant solutions may have diminished the sensitivity of the assay, especially at the 0.5 ml/plate level.

Reliability : (2) valid with restrictions
29.10.2002 (43)

Type : Salmonella typhimurium reverse mutation assay
System of testing : TA98, TA100, TA1535, TA1537
Test concentration : 25, 75, 225, 675, 2025 ug/plate
Cycotoxic concentr. : >2025 ug/plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1981
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The metabolic activation system was prepared from rat liver microsomes.
Remark : At the concentrations of 675 and 2025 µg/0.1 mL the test material precipitated in soft agar.
Method: Ames et al.1973, 1973, and 1975
Test substance : Reoplast 39 (oxirane oxygen 6.4%, iodine value 4.3) is 100% Epoxidized Soybean Oil
Reliability : (2) valid with restrictions
01.12.2003 (6) (14)

Type : Ames test
System of testing : Salmonella typhimurium
Test concentration :
Cycotoxic concentr. :
Metabolic activation : with and without
Result : negative
Method : other
Year : 1982
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : The source of the metabolic activation system was not specified.
Test substance : Unspecified grade of ESBO
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
18.05.2004 (5) (6) (31)

Type : Cytogenetic assay
System of testing : Human lymphocyte cultures
Test concentration : 1.554-55 ug/ml
Cycotoxic concentr. : >55 ug/ml
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 473
Year : 1992
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The positive control chemicals were dissolved in sterile anhydrous analytical grade dimethyl sulphoxide:

4-Nitroquinoline-1-oxide, Cyclophosphamide

The mammalian liver post-mitochondrial fraction (S-9) used for metabolic activation was prepared from male Sprague Dawley rats induced with Aroclor 1254.

An appropriate volume of whole blood was drawn from the peripheral circulation of 2 healthy, non-smoking volunteers (male in Experiment 1 and female in Experiment 2) on the day cultures were established in sterile disposable centrifuge tubes.

Blood cultures were incubated at 37°C for approximately 48 hours. S-9 mix or KCl were added. One set of quadruplicate cultures (A, B, C and D) for each of the 2 sampling times was treated with the solvent. One set of duplicate cultures was treated with the test chemical or remained "untreated" receiving 0.1 ml culture medium alone. Further duplicate cultures for sampling at the first harvest only, were treated with 0.1 ml of the positive control chemicals.

Treatment media remained on cultures not receiving S-9 until sampling, that is 20 hours and 44 hours after the beginning of treatment. Cultures were treated in the presence of S-9 for 3 hours only. Cultures were incubated for a further 17 or 41 hours before harvesting. The delayed sample was adopted for test and negative control cultures only, not for positive controls.

Colchicine was added to arrest dividing cells in metaphase. Lymphocytes were kept in fixative in the refrigerator at approximately 4°C before slides were prepared, stained, rinsed, dried and mounted with coverslips.

Slides were examined, uncoded, for mitotic index (MI) or percentage of cells in mitosis. Slides from sufficient treatments were scored to determine if chemically induced mitotic inhibition had occurred. This is defined as a clear decrease in mitotic index compared with negative controls (based on at least 1000 cells counted), preferably dose-related.

The top dose for analysis was a concentration close to the solubility limit in the treatment medium. Of the cultures harvested at 20 hours, in Experiment 1 those receiving the selected top dose and the next 2 lower doses were to be analysed. If a negative or equivocal result was obtained in this experiment, a delayed (44 hour) harvest was included in Experiment 2. Three dose levels were chosen for analysis at the first sampling time and a single dose level at the delayed sampling identified from the mitotic index data of either the first or second sampling. Slides from negative control cultures were analysed only if frequencies of aberrant cells in solvent control cultures exceeded normal ranges.

One hundred metaphases from each culture were analysed for chromosome aberrations. Only cells with 44-46 chromosomes were considered acceptable for analysis of structural aberrations. Classification of aberrations was based on the

scheme described by ISM. Observations were recorded on raw data sheets with the microscope stage coordinates of any aberrant cell.

After completion of scoring, slides were decoded. The aberrant cells in each culture were categorised as follows: 1) cells with structural aberrations including gaps, 2) cells with structural aberrations excluding gaps, and 3) polyploid, endoreduplicated or hyperdiploid cells.

The totals for category 2 in negative control cultures were used to determine whether the assay was acceptable. The proportions of aberrant cells in each replicate were used to establish acceptable heterogeneity between replicates by means of a binomial dispersion test.

The proportion of cells in category 2 for each test treatment condition were compared with the proportion in negative controls using Fisher's exact test. Probability values of $p < 0.05$ were accepted as significant. The proportions of cells in categories 1 and 3 were examined in relation to historical control (normal) ranges.

The human lymphocyte assay was to be considered valid if the following criteria were met:1) the binomial dispersion test demonstrated acceptable heterogeneity between replicate cultures; 2) the proportion of cells with structural aberrations (excluding gaps) in negative control cultures fell within the normal range; 3)at least 160 cells out of an intended 200 were analysable at each treatment level; 4) the positive control chemicals induced statistically significant increases in the number of cells with structural aberrations.

The test chemical was to be considered as clearly positive in this assay if: 1) statistically significant increases in the proportion of cells with structural aberrations (excluding gaps) occurred at one or more concentrations, 2) the proportion of aberrant cells at such data points exceeded the normal range, and 3) the results were confirmed in the second experiment.

Increases in numbers of cells with gaps or increases in the proportions of cells with structural aberrations not exceeding the normal range or occurring only at very high or very toxic concentrations were likely to be concluded as "equivocal". Full assessment of the biological importance of such increases is likely only to be possible with reference to data from other test systems. Cells with exchange aberrations or cells with greater than one aberration were to be considered of particular biological significance. A positive result only at the delayed harvest in Experiment 2 was to be taken as evidence of clastogenicity provided criteria 1 and 2 were met.

Remark : # cells Structural aberrations with / without gaps

Hours:		20	20	20	20	44	44
S-9:		-	+	-	+	-	+
Solv	100	9/3	1/0	4/1	3/1	0/0	2/0
control	100	3/2	0/0	6/4	1/0	9/5	0/0

26.95	100	1/0	5/2*				
µg/ml	100	0/0	2/2				
30.94	100			4/1	1/1		
	100			3/0	1/1		
38.5	100	1/0	2/0				
	100	2/1	2/0				
41.25	100			6/5	0/0		
	100			6/5	4/4		
55	100	5/2	2/1	3/2	0/0	2/1	2/0
	100	4/2	4/1	2/1	2/1	2/1	1/0
pos.	25	13/11**	8/7**	8/8**	8/8**		
control	25	12/10	7/3	9/8	14/11		

% with numerical aberrations

Hours:	20	20	20	20	44	44
S-9:	-	+	-	+	-	+
Solv	1	0	1	2	2	0
control	1	0	0	0	0	0
26.95	3	1				
µg/ml	1	1				
30.94			0	0		
			0	0		
38.5	1	0				
	0	0				
41.25			1	0		
			4	1		
55	0	0	2	0	2	0
	0	0	0	0	2	0
Pos	0	0	0	0		
control	0	0	0	0		

* p < or = 0.05 **

SUMMARY

Epoxidised soybean oil was tested in an in vitro cytogenetics assay using duplicate human lymphocyte cultures from a male and female donor in 2 independent experiments. The highest dose level used, 55 ug/ml, was close to the solubility limit of epoxidised soybean oil in culture medium. Treatments covering a broad range of doses, separated by narrow intervals, were performed both in the absence and presence of metabolic activation by a rat liver post-mitochondrial fraction (S-9) from Aroclor 1254 induced animals. In Experiment 1, treatment in the absence of S-9 was continuous for 20 hours. Treatment in the presence of S-9 was for 3 hours only followed by a 17 hour recovery period prior to harvest. The test compound dose levels for chromosome analysis were selected by evaluating the effect of epoxidised soybean oil on mitotic index. Chromosome aberrations were analysed at 3 consecutive dose levels. The highest concentration chosen for analysis at this time, 55ug/ml, induced no mitotic inhibition in the absence of S-9 and approximately 14% in its presence, although this was not clearly dose-related. Experiment 2 included a delayed sampling time. Treatment in the absence of S-9 was continuous for 20 or 44 hours. Treatment in the presence of

S-9 was for 3 hours followed by a 17 or 41 hour recovery period. The highest concentration chosen for analysis at 20 hours, was again 55 ug/ml which on this occasion induced approximately 47% and 25% mitotic inhibition in the absence and presence of S-9, respectively. The effect of this single concentration only was investigated at the delayed harvest at which time no mitotic inhibition was induced.

Appropriate negative (solvent and untreated) control cultures were included in the test system in both experiments at both sampling times. Acceptable numbers of cells with structural aberrations were observed in solvent control cultures, slides from untreated cultures were not analysed. 4-Nitroquinoline 1-oxide (NQO) and cyclophosphamide (CPA) were employed as positive control chemicals in the absence and presence of liver S-9, respectively. Cells receiving these were sampled in each experiment 20 hours after the start of treatment; both compounds induced statistically significant increases in the proportion of cells with structural aberrations.

In most cases, treatment of cultures with epoxidised soybean oil in either the absence or presence of S-9 resulted in frequencies of cells with aberrations which were similar to and not significantly different from those seen in concurrent negative controls. Small increases in cells with aberrations were seen at the 20 hour sampling time following treatment with 26.95 ug epoxidised soybean oil/ml in the presence of S-9 in Experiment 1 and 41.25 ug epoxidised soybean oil/ml in the absence of S-9 in Experiment 2. In neither case, however, was the increase characterized by both statistical significance and frequencies of aberrant cells outside negative historical control ranges and could not therefore be considered biologically important.

Result : The results of mitotic index determinations for the treatments in Experiment 1, without and with S-9 sampled at 20 hours were as follows:

No mitotic inhibition was observed in the absence of S-9 and little (approximately 14%) in its presence, although this was not clearly dose-related. The following doses were selected for analysis:

20 hours, - S-9:	26.95, 38.5, 55 ug/ml	0%	
20 hours, + S-9:	26.95, 38.5, 55 ug/ml	-	14%

In contrast to Experiment 1, mitotic inhibition was observed in the absence of S-9 at the 20 hour sampling in Experiment 2. Approximately 47% mitotic inhibition was seen at the highest dose level in the absence of S-9 and 25% in its presence. No mitotic inhibition was seen at the 44 hour sampling time. The following doses were selected for analysis:

20 hours,	- S-9:	30.94, 41.25, 55 ug/ml	47%
20 hours,	+ S-9:	30.94, 41.25, 55 ug/ml	25%
44 hours,	- and + S-9:	55 ug/ml	0%

Acceptance criteria were met.

Structural aberrations: in most cases, treatment of cultures with epoxidised soybean oil in either the absence or presence of S-9 resulted (at both sampling times) in frequencies of cells with aberrations, which were similar to and not significantly different from those seen in concurrent negative controls. A small, but statistically significant increase in cells with aberrations was seen at the 20 hour sampling time following treatment with 26.95 ug epoxidised soybean oil/ml in the presence of S-9 in Experiment 1 but the numbers of aberrant cells observed did not exceed the normal range. Similarly, numbers of cells with aberrations following treatment with 41.25 ug/ml in the absence of S-9 for 20 hours in Experiment 2 exceeded the normal range but the total increase was not statistically significant. In neither case, therefore, was the observation considered to be biologically important.

Numerical aberrations: No reproducible increases in numbers of cells with numerical aberration were observed under any treatment /sampling conditions.

Source : ATOFINA Chemicals
Epona Associates, LLC Willington, CT
ATOFINA Chemicals Inc. Philadelphia

Test substance : Reoplast 39 (oxirane oxygen 6.4%, iodine value 4.3) is 100% Epoxidized Soybean Oil

Conclusion : It is concluded that epoxidised soybean oil was unable to induce chromosome aberrations in cultured human peripheral blood lymphocytes when tested to its limit of solubility in both the absence and presence of S-9.

Reliability : (1) valid without restriction
18.05.2004 (6) (28)

Type : Mammalian cell gene mutation assay
System of testing : Mouse: lymphoma cells (tk +/- locus of L5178Y)
Test concentration : 312.5 - 5000 ug/ml (two separate tests)
Cycotoxic concentr. : >5000 ug/ml
Metabolic activation : with and without
Result : negative
Method : OECD Guide-line 476
Year : 1992
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Acetone was used as the solvent and following addition of the test chemical, the cultures were vortexed (for approximately 10 seconds) to obtain a good emulsion. A top dose of 5000 ug/ml was achievable using an emulsion. There was no significant increase in osmolality (> 50 mOsm/kg) in cultures treated with ESBO at the top dose of 5000 ug/ml.

Negative controls comprised treatments with the solvent, acetone, diluted 100-fold in the treatment medium. A non-vortexed control culture was included in the range-finder experiment (- S-9) to confirm that vortexing would have no adverse effect on the cell cultures. The positive control chemicals were 4-nitroquinoline-1-oxide(NQO) and benzo(a)pyrene (BP) All solutions were prepared in anhydrous analytical grade dimethyl sulphoxide (DMSO). The mammalian liver post-mitochondrial fraction (S-9) used for metabolic

activation was prepared from male Sprague Dawley rats, induced with Aroclor 1254.

Cell cultures: L5178Y TK +/- mouse lymphoma cells

Cytotoxicity range-finder: Single cultures only were used and positive controls were not included. An additional non-vortexed control culture was also included (- S-9) in the range-finder experiment.

Statistical significance of mutant frequencies (total wells with clones) was carried out according to the UKEMS guidelines. Thus the control log mutant frequency (LMF) was compared with the LMF from each treatment dose, and secondly the data were checked for a linear trend in mutant frequency with treatment dose. These tests required the calculation of the heterogeneity factor to obtain a modified estimate of variance.

The assay was considered valid if the following criteria were met: 1) the mutant frequencies in the negative (solvent) control cultures fell within the normal range and 2) at least 1 concentration of each of the positive control chemicals induced a clear increase in mutant frequency. The mutant frequencies obtained in this study for the negative control cultures were slightly high but within the recommended limits for this assay. Furthermore, the positive control chemicals induced a clear increase in mutant frequency at all doses tested.

Evaluation criteria: The test substance was considered to be mutagenic if: 1) the assay was valid, 2) the mutant frequency at 1 or more doses was significantly greater than that of the negative control, 3) there was a significant dose-relationship as indicated by the linear trend analysis, and 4) the effects described above were reproducible.

Remark :

Mutant frequency

S-9	-		+	
µg/ml	Trial 1	Trial 2	Trial 1	Trial 2
0	313	411	402	305
312.5	390	335	485	331
625	326	466	563	331
1250	440	405	519	314
2500	520*	461	426	283
5000	468*	--	434	311
Pos control	1677	1136	1795	884

* Significance at 5%
-- Excluded due to excessive heterogeneity

% RS ranged from
SUMMARY
Epoxidised Soybean Oil (ESBO) was assayed for its ability to induce mutation at the tk locus

(5-trifluorothymidineresistance) in mouse lymphoma cells using a fluctuation protocol. The study consisted of a cytotoxicity range finder followed by 2 independent experiments, each conducted in the absence and presence of metabolic activation by an Aroclor 1254 induced rat liver post-mitochondrial fraction (S-9). Following a wide range of treatments in the range-finder experiment, separated by 2-fold intervals and ranging from 78.125 to 5000 ug/ml, cells survived all doses of ESBO yielding 109% relative survival in the absence and 100.0% relative survival in the presence of S-9 at the top dose. Accordingly, 5 doses were chosen for the first experiment, separated by 2-fold intervals and ranging from 312.5 to 5000 ug/ml. All doses were plated for viability and 5-trifluorothymidine resistance 2 days after treatment. The top doses plated yielded 143.9% and 178.7% relative survival in the absence and presence of S-9. In the second experiment the same dose range was selected. The top dose plated in this experiment was again 5000 ug/ml in the absence and presence of S-9, which yielded 100.7% and 83.2% relative survival, respectively.

Negative (solvent) and positive control treatments were included in each experiment in the absence and presence of S-9. Mutant frequencies in negative control cultures fell within normal ranges, and statistically significant increases in mutation were induced by the positive control chemicals 4-nitroquinoline 1-oxide (without S-9) and benzo(a)pyrene (with S-9). Therefore the study was accepted as valid.

In the absence of S-9, reproducible statistically significant and dose-related increases in mutant frequency were not observed in the 2 experiments over the dose range 312.5 to 2500 ug/ml. At 5000 ug/ml, a positive point was obtained in Experiment 1 and due to heterogeneity in the data this dose was excluded from analysis in Experiment 2. However, if each of the replicate cultures at 5000 ug/ml in Experiment 2 are considered in turn, neither yields a statistically significant increase in mutant frequency. This, combined with the fact that there were no absolute increases in mutant numbers in Experiment 1 at 5000 ug/ml and that carry-over of the test compound was a problem at this dose, suggests that the increased mutant frequency seen in Experiment 1 was not the result of chemically induced mutation.

In the presence of S-9, no statistically significant increases in mutant frequency were observed at any dose level tested in Experiment 1 or 2.

Result : In the cytotoxicity range-finder experiment up to 5000 ug/ml no marked toxicity was observed following treatment with ESBO.

5 doses were selected for Experiment 1 ranging from 312.5 to 5000 ug/ml. An emulsion was formed at all doses tested. At the top dose of 5000 ug/ml relative survival values of 143.9% and 178.7% were obtained in the absence and presence of S-9, respectively. The dose range selected for Experiment 2 was identical to that used in Experiment 1. No toxicity

was observed, and the relative survival values obtained at the top dose of 5000 ug/ml were 100.7% and 83.2% in the absence and presence of S-9, respectively. The acceptance criteria were met and the study was accepted as valid.

In the absence of S-9 in Experiment 1, statistically significant increases in mutant frequency were observed at 2500 and 5000 ug/ml, which seemed attributable to slightly depressed viability counts, rather than any clear increase in the absolute number of mutants. In Experiment 2 no significant increases in mutant frequency were observed and no dose-response was indicated in the absence of S-9 over the dose range 312.5 to 2500 ug/ml. In both experiments at 5000 ug/ml, the cultures were counted using a haemocytometer due to the persistence of test compound. Excessive heterogeneity was observed between the replicate cultures for the viability and mutant plates at this dose in Experiment 2 and the data were excluded from analysis. The data obtained for ESBO in the absence of S-9 do not fulfill the criteria for a mutagenic response. Reproducible, statistically significant and dose-related increases in mutant frequency were not observed in the 2 experiments over the dose range of 312.5 to 2500 ug/ml. At 5000 ug/ml, a positive point was obtained in Experiment 1 and due to heterogeneity in the data this dose was excluded from analysis in Experiment 2. If each of the replicate cultures at 5000 ug/ml in Experiment 2 are considered in turn, neither yields a statistically significant increase in mutant frequency. This, combined with the fact that there were no absolute increases in mutant numbers in Experiment 1 at 5000 ug/ml and that carry-over of the test compound was a problem at this dose, suggests that the increased mutant frequency seen in Experiment 1 was not the result of chemically induced mutation. In the presence of S-9, no statistically significant increases in mutant frequency were observed at any dose level of ESBO tested in Experiment 1 or 2. For the negative and positive controls, the number of wells containing small colonies and the number containing large colonies were scored. Thus the small and large colony mutant frequencies could be estimated and the proportion of small mutant colonies could be calculated. For the negative controls, the proportion of small colony mutants in the absence and presence of S-9 ranged from 66% to 67% in Experiment 1 and from 53% to 56% in Experiment 2. A higher proportion of small colony mutants was observed following treatment with the positive control chemicals NQO and BP. Small and large colony mutant frequencies are not reported for ESBO as the data obtained did not fulfill the criteria for a mutagenic response.

Source : Ciba Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
ATOFINA Chemicals, Inc.
Epona Associates, LLC Willington, CT
ATOFINA Chemicals Inc. Philadelphia

Test substance : Reoplast 39 (oxirane oxygen 6.4%, iodine value 4.3). Epoxidised Soybean Oil, a yellow liquid.

Conclusion : It is concluded that, under the conditions employed in this study, ESBO failed to demonstrate an ability to induce mutation at the tk locus of L5178Y mouse lymphoma cells in the absence and presence of S-9.

Reliability : (1) valid without restriction
18.05.2004 (6) (30)

Type : Mammalian cell gene mutation assay
System of testing : hamster: CHO cells (HGPRT locus)
Test concentration : 0.2-2 mg/ml
Cycotoxic concentr. : with S-9: >2mg/ml; without S-9: >/= 0.5 mg/ml
Metabolic activation : with and without
Result : negative
Method : other
Year : 1987
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : The metabolic activation system was derived from Aroclor 1254-induced rat liver homogenate.
Remark :

Mean Mutation Frequency x 10-6

µg/ml	- S-9	+ S-9
0	6.1	0.9
200	5.5	0.0
500	0.7	4.6
1000	14.1	2.6
2000	0.9	3.4

Pos 165.5
In the absence of S-9, significant cytotoxicity (> 50% cell killing) was observed at 0.5, 1.0 and 2.0 mg/ml. No significant cytotoxicity was observed in the presence of S9.
Source : Epona Associates, LLC Willington, CT
ATOFINA Chemicals Inc. Philadelphia
Reliability : (2) valid with restrictions
18.05.2004 (44)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

Species : rat
Sex : male/female
Strain : Wistar
Route of admin. : oral feed
Exposure period : 24 months
Frequency of treatm. : daily
Post exposure period : none
Doses : 0.025, 0.25 and 2.5% [2.5 % ~ 1000 mg/kg (males), 1400 mg/kg (females)]
Result : negative
Control group : other: control and SBO treated animals run concurrently
Method : other
Year : 1986
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 48 male and 48 female rats were given up to 2.5% ESBO in the diet for two years. The usual parameters for a

lifetime toxicity-oncogenicity study were measured. Body weight, food and water consumption, clinical signs of toxic effects, and mortality were followed throughout the study. Hematological examinations were made using blood samples from 10 rats of each sex from the control, the two highest dose ESBO, and the SBO treatments at 3, 6, 12 and 18 months and from all rats surviving at the end of the study. Serum separated from the blood samples taken at the end of the study was used for biochemical analyses. Urine samples were collected from 10 animals of each sex from the control and 2.5% ESBO groups at 3 months, and from the control, the 0.25 and 2.5% ESBO and the 2.5% SBO treatment groups at 6, 12, 18, and 24 months. After 104 weeks, all surviving rats were killed and subjected to a complete gross pathological examination and a preselected battery of tissues taken for microscopic examination.

Remark : Control group: Concurrent treatment with basal diet or diet supplemented with 2.5% Soya Bean Oil (SBO) (48/sex/group)

Result : There was no adverse effect on survival. The males given 2.5% ESBO gained more weight than the controls, while the females were slightly lighter. The same rats consumed slightly less food than controls, the difference being greater in females (approximately 1 g/rat/day) than males (approximately 0.5 g/rat/day). The water intake of the females given 2.5% ESBO was lower than the control, especially in the second year of the study. Hematological examination and investigations of urine at 3, 6, 12, 18 and 24 months did not reveal any adverse effects. A lower volume of more concentrated urine was excreted by the females given 2.5% ESBO compared with the controls, with occasional increases in urinary cell excretion. The organ weights in females were similar to controls, while in males given 2.5% ESBO, and more noticeably in those given 2.5% SBO, several organs were heavier than control. This was related to the growth changes since when expressed relative to body weight the value were normal. The incidence of histological findings, including tumors, was similar in treated and control groups. There was a tendency for less severe glomerulonephrosis in the ESBO-treated rats. There was a marginally increased incidence of uterine changes in the females given 2.5% ESBO. Since there were similar changes in the females given SBO, these changes could not be clearly related to ESBO. It was concluded that ESBO was not carcinogenic when fed to rats at up to 2.5% of the diet. Further, it was concluded that the no-adverse-effect level was 2.5% providing an average daily intake of approximately 1.0 g/kg in males and 1.4 g/kg in females.

Test substance : ESBO (oxirane oxygen 6.3-6.4%, iodine number 7-8)
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
03.10.2005 (4) (6)

Species : rat
Sex : male/female
Strain : no data
Route of admin. : oral feed
Exposure period : 1 or 2 years
Frequency of treatm. : daily
Post exposure period : no data
Doses : up to 5% (approximately 2.5 g/kg bw/day)

Result : negative
Control group : yes
Method : other
Year : 1960
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Groups of 15 male and female rats were given Paraplex G-60 or G-62 in the diet at 0, 0.1, 0.5, 1.0, 2.5, and 5.0%. The rats were individually caged and weighed once weekly. Each group of 15 was subdivided into subgroups of 5 and 10 animals. The groups of 5 were sacrificed at the end of one year (Paraplex G-60) or six months (Paraplex G-62) and subjected to histopathologic studies and organ to body weight measurements (liver, kidney and testes). In addition, animals fed Paraplex G-62 were subjected to blood studies at the 6 months sacrifice. The groups of ten animals were exposed for two years. Blood studies were conducted at 11 and 24 months. Histopathologic studies were conducted on survivors at two years in the 2.5 and 5% dose groups and controls.

Remark : Specifications for Paraplex G62 and G60 composition:

	Typical Spec limits	Spec limits G62	Spec limits G60
Acid Value mg KOH/g	0.3	0 - 1.0	0-0.5
Iodine Value	10	6 - 14	0-1.1
Oxirane Oxygen	6.5	6.3 (max not given)	6.8 (max not given)

Result : Paraplex G-60: There was no definitive effect on survival. There was an early depression of growth at 5% Paraplex G-60. There was no effect on hematological values. Male rats receiving 5% Paraplex G-60 had significantly elevated liver to body weight ratios. There were no treatment-related histopathologic lesions. There was no evidence of carcinogenicity.
Paraplex G-62: There was no definitive effect on survival. Among female rats fed Paraplex G-62, growth was depressed during the early portion of the study, with no effect observed by 8 weeks. There was no effect on hematological values. Females receiving 0.5% Paraplex G-62 and males receiving >2% Paraplex G-62 had significantly elevated liver to body weight ratios. Increased kidney to body weight ratios were observed for females receiving >1.5% Paraplex G-62. There were no treatment-related histopathologic lesions. There was no evidence of carcinogenicity.

Test substance : Paraplex G-60 or Paraplex G-62 are 100% epoxidized soybean oil
The grade of ESBO used in this study does not match the specification of modern commercial ESBO grades.

Reliability : (2) valid with restrictions
16.12.2003 (6) (37) (53) (54)

Species : mouse
Sex :
Strain : C3H
Route of admin. : dermal
Exposure period : Up to 24 months
Frequency of treatm. : Three days per week
Post exposure period : Up to 17 months
Doses : One brush full of undiluted test article/application
Result : negative
Control group :
Method : other
Year : 1963
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Hair was removed with electric clippers, as needed, from the backs of a group of 40 90-day old mice. Three applications per week of one brush full of test article was applied to the midline of the back on Monday, Wednesday and Friday. Observations for papillomas and carcinomas were made during each painting period. Groups of 30 to 40 mice were used. The mice were observed until death.
Result : Thirty-six animals were alive at one year, and 26 animals were alive at 17 months but none were alive at two years. No skin tumors were observed.
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
18.05.2004 (5) (6) (40) (57)

Species : rat
Sex : no data
Strain : no data
Route of admin. : gavage
Exposure period : up to 1 year
Frequency of treatm. : 5 days/week
Post exposure period : no data
Doses : 100 mg/day
Result : ambiguous
Control group : no data specified
Method : other
Year : 1965
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Result : "Treatment" may have a slight enhancing effect" on the activity of a liver carcinogen given at the same time.
Test substance : neat ESBO
Reliability : (4) not assignable
Reliability of 4 assigned because the documentation is insufficient for assessment.
18.05.2004 (5) (6) (58)

Species : mouse
Sex : no data
Strain : no data
Route of admin. : i.p.

Exposure period	:	3 weeks
Frequency of treatm.	:	weekly
Post exposure period	:	16 weeks
Doses	:	total dose = 2.15 g/kg bw
Result	:	negative
Control group	:	yes
Method	:	other
Year	:	1958
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Thirty mice were injected i.p. weekly for three weeks and examined for lung tumors after 16 weeks. Mice were also subjected to gross examination of a range of unspecified tissues. Positive control group treated similarly with a potent carcinogen.
Remark	:	Sites other than the lung were not examined.
Result	:	No increase in the incidence of lung tumors in treated animals. Positive control animals showed almost 100% lung tumor incidence.
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

18.05.2004 (5) (6) (32)

5.8.1 TOXICITY TO FERTILITY

Type	:	One generation study
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	Pretreatment: 71 days in males; 15 days in female; then F0 male and female rats paired. Treatment continued in females during the mating, pregnancy and lactation until day 21 post-partum (PP) and in males until day 21 PP of F1 litters.
Frequency of treatm.	:	daily
Premating exposure period		
Male	:	71 days
Female	:	15 days
Duration of test	:	Until day 21 post-partum of F1 litters
No. of generation studies	:	
Doses	:	100, 300 and 1000 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL parental	:	>= 1000 mg/kg bw
NOAEL F1 offspring	:	>= 1000 mg/kg bw
Method	:	OECD Guide-line 415 "One-generation Reproduction Toxicity Study"
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	O.E.C.D. guideline No. 415, 26th May 1983, E.E.C. Recommendation No. 87/302/E.E.C., 18th November 1987 The test substance EPOXIDIZED SOYBEAN OIL (ESBO) was given daily 7 times a week to 3 groups of 28 F0 male and 28 F0 female Sprague-Dawley rats by gavage at the dose levels of

100, 300 and 1000 mg/kg bw/day. The F0 control animals (28 males and 28 females) received the vehicle Soybean Oil (SBO).

After 71 days of treatment in males and 15 days of treatment in females, the F0 male and female rats were paired.

Each male was paired with one female of the same treatment group for the night. The female was placed with the same male until mating occurred or 10 days had elapsed. If no evidence of mating was observed after 10 days, the female was placed after 3 days rest period with another male that had already successfully mated, until mating occurred or 11 days had elapsed. Each morning, a vaginal lavage was performed in order to detect the presence of spermatozoa. The day when spermatozoa were found was designated as day 0 of pregnancy.

Treatment was continued in females during the mating and pregnancy and lactation periods until day 21 post-partum and in males during the mating period until day 21 post-partum of F1 litters.

F0 animals were observed daily for clinical signs. Any animal showing signs of poor clinical condition, especially if death appeared imminent, was asphyxiated by carbon dioxide and killed by exsanguination. Any animal found dead or killed due to poor clinical condition was subjected to macroscopic examination and a full spectrum of tissues was preserved whenever possible.

The quantity of food consumed by each male was recorded once a week over a 7-day period of treatment until sacrifice. The quantity of food consumed by each female was recorded as follows:
during the premating period, once a week over a 7-day period,
during pregnancy, at the intervals day 0-day 7, day 7-day 14 and day 14-day 20,
during lactation, at the intervals day 1 pp-day 7 pp, day 7pp-day 14 pp and day 14 pp-day 21 pp.

However, food consumption was not measured during the mating period. Food intake per animal and per day was calculated using the amount of food given and left in each feeder. Body weight was recorded for each males on the first day of treatment (day 1) and then once a week until sacrifice.

Body weight was recorded for each females on the first day of treatment (day 1), once a week before mating and during mating periods, on days 0, 7, 14 and 20 of pregnancy, and on days 1, 7, 14 and 21 post-partum.

The females were allowed to deliver normally. The F1 litters were examined daily for clinical signs, viability, physical and reflex development until day 21 post-partum. Pup body weights were recorded on days 1, 4, 7, 14 and 21 post-partum (each pup was identified by tattoo).

On day 4 post-partum, the size of each litter was adjusted

by eliminating extra pups by random selection, as nearly as possible, at 4 males and 4 females per litter. Whenever, the number of male or female pups prevented having at least 4 of each sex per litter, partial adjustment (for example, 5 males and 3 females) was made. Adjustments were not made for litters of less than 8 pups.

The number of pups in each litter exhibiting the following characteristics was recorded:
on day 5 post-partum: pinna unfolding, hair growth, surface righting reflex
on day 11 post-partum: cliff avoidance
on day 13 post-partum: incisor eruption
on day 17 post-partum: eye opening, auricular duct opening, air righting reflex

About 24 hours after the last administration, hematology and blood chemistry investigations were performed in 5 males and 5 females of each group.

At the end of the study, macroscopic examination of all F0 males and females and F1 pups was performed. In all the parents, reproductive organs and macroscopic lesions were sampled and additionally in 5 males and 5 females of each group ileum, kidneys and liver were sampled.

Microscopic examination of the reproductive organs was performed in all animals of the control and 1000 mg /kg bw/day groups and in animals suspected of infertility, those that died or were sacrificed in the 100 and 300 mg/kg bw/day groups. In addition the livers of one male of the 1000 mg/kg bw/day group and of the control group were also examined microscopically.

Statistical analysis: Mean values were compared by one-way variance analysis and Dunnett's test. Percentage values were compared by Fisher's exact probability test.

The following sequence was used for the statistical analysis of haematology and blood biochemistry data:
The normality of the distribution of the values in each group was checked by Komolgorov Smirnov's test (1948). If the distribution was normal, the homogeneity of variances between the groups was assessed by Bartlett's test (1937)(more than 2 groups) or Fisher's test (1934) (2 groups). If no significant heterogeneity of the variances was established, the comparison between treated and control groups was performed by Dunnett's test (1955). If the variances were heterogeneous, the comparison between treated and control groups was performed by Dunn's test (1964) (more than 2 groups) or by Mann Whitney's test (1947) (2 groups). If the distribution of values in the group was not normal, the analysis was repeated after logarithmic transformation of the values. If this logarithmic transformation fails to normalise the distribution of the values, comparison of treated and control groups was performed by Dunn's test using original values.

Result : Summary: No treatment related mortalities or clinical signs were observed. The mean food consumption and body weight gain of males and females were similar in the control and

treated groups. The variations of hematologic or blood chemistry parameters were not of toxicological importance. The macroscopic and microscopic examination of the animals did not reveal any changes attributed to the treatment.

Reproductive data: The mating and fertility indices of males and females were similar in the control and treated groups.

Litter data: The gestation index and the mean duration of gestation were similar in all groups. The live birth index was 100% in all groups. The viability indices on day 4 and day 21 post-partum, the physical and reflex development of pups and the mean pup body weight were similar in the control and treated groups.

Details: Mating Males: The mating index of males was similar in the control group (96.4%) and the 100 (89.3%), 300 (96.4%) and 1000 (96.4%) mg/kg bw/day groups. Females: The mating index of females was 100 % in the control group and the 100 and 300 mg/kg bw/day groups. It was 96.4% in the 1000 mg/kg bw/day group as 1 female did not mate. This is not related to the treatment.

Fertility Males: The fertility index of males was similar in the control group (81.5%) and the 100 (88.5%), 300 (92.6%) and 1000 (100.0%) mg/kg bw/day groups. Females: The fertility index of females was similar in the control group (82.1%) and the 100 (92.9%), 300 (92.9%) and 1000 (100.0%) mg/kg bw/day groups.

Gestation: The mean number of implantation sites was similar in the control and treated groups. The gestation index was 100% in the control, 300 and 1000 mg/kg bw/day groups. In the 100 mg/kg bw/day group, it was 96.2% as one pregnant female was sacrificed on day 9 of pregnancy (due to a misdosing). The mean duration of gestation was similar in all groups and within the normal range of 21-22 days. The live birth index was 100 % in all groups.

Pups: The viability index on day 4 post-partum was similar in the control (94.2%) and the 100 (91.1 %), 300 (97.9%) and 1000 (93.5%) mg/kg bw/day groups. On day 21 post-partum, the lactation index was also similar in the control (97.8%) and the 100 (98.9%), 300 (97.9%) and 1000 (94.4%) mg/kg bw/day groups.
The physical development and reflex development were similar in the control and treated groups.
No clinical signs attributed to the treatment were observed in pups of any group.
No treatment-related macroscopic changes were noted in pups sacrificed at the end of the study. In pups culled on day 4 post-partum, no macroscopic changes were noted in the control and the 100 mg/kg bw/day groups. In the 300 and 1000 mg/kg bw/day groups I out of 208 (0.5%) pups and 6 out of 203 (3.0%; $p < 00.5$) pups had a dilated renal pelvis. In the 1000 mg/kg bw/day group, 5 out of the 6 affected pups provided from the same litter whose mother was found dead on day 7 postpartum. This litter had a mean body weight lower than that of the other litters of the same group.

Consequently the dilatation of renal pelvis of these pups is related to their slight delayed development related itself to the clinical conditions of the mother. This dilatation of renal pelvis is not attributed to the treatment.

Haematology: The statistically significant differences noted between control and treated animals in some haematological parameters, namely total white and red blood cell count in males, were considered to be of no toxicological importance as they were minor, not dose-related and the individual values were within the range of our background data (white blood cells: 5.9 - 15.6 G/l; red blood cells: 8.05 - 9.80T/1).
No perceptible differences between control and treated animals in the other parameters.

PATHOLOGY: Macroscopic examination: Liver enlargement, without any relevant histopathological findings, was noted in 1 out of 28 males given 1000 mg/kg bw/day. Paleness of the liver was found in 2 out of 28 males given 300 mg/kg bw/day. These findings were considered to be of spontaneous nature and irrelevant to the treatment with the test substance. The other macroscopic findings encountered were those which are commonly recorded spontaneously in the rat of this strain and age and were considered to be of no toxicological importance.

Microscopic examination: Regular oestrous cycle, as evidenced from the morphological changes in the ovaries, uterus and vagina, was noted in the control and treated female rats, except in 2 females given 100 mg/kg bw/day. In these two animals deciduomatosis was noted in one female; severe metritis and degenerated placenta were noted in the other female. These changes can be found in untreated rats, therefore this weak incidence is not considered of toxicological importance.
No treatment-related abnormalities were found in the male genital organs of the animals examined.

Source : Ciba Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
ATOFINA Chemicals

Test substance : Reoplast 39 (oxirane oxygen 6.4%, iodine value 4.3) is 100% Epoxidized Soybean Oil

Conclusion : The test substance ESBO administered daily by the oral route (gavage) to male and female Sprague-Dawley rats at the 100, 300 and 1000 mg/kg bw/day dose levels 71 days before mating in males and 15 days before mating in females until day 21 post-partum of F1 litters did not induce any toxic effects in parent males and females, did not disturb their capacity of reproduction and did not impair the development of the F1 offspring.
Under the experimental conditions, the highest tested dose of 1000 mg/kg bw/day was found to be the No Observed Effect Level.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

05.08.2005 (6) (19)

Type : other

Species : rat

Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	Treatment began 15 days before mating and up to day 7 post-partum
Frequency of treatm.	:	daily
Premating exposure period		
Male	:	Treatment began 15 days before mating
Female	:	Treatment began 15 days before mating
Duration of test	:	Up to day 7 post-partum
No. of generation studies	:	
Doses	:	150, 450, and 1000 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL parental	:	= 1000 mg/kg bw
NOAEL F1 offspring	:	= 1000 mg/kg bw
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Groups of 12 male and 12 female rats were given up 1000 mg/kg bw/day by gavage. Treatment began 15 days before mating and continued through mating and pregnancy for half the female animals. Treatment continued through lactation and until day 7 post-partum of F1 litters for the other half of the females. Treatment continued for the males through day 7 post-partum. F0 animals were observed daily for clinical signs. Food consumption and body weights were measured at designated intervals. On day 20 of pregnancy, half the females per group were sacrificed, examined macroscopically and fetuses removed by caesarean section. Litter parameters included number of corpora lutea, implantation sites, resorptions, dead and live fetuses. Fetuses were weighed, sexed and examined. The other females were allowed to deliver normally, and F1 litters were examined daily for clinical signs and viability until day 7 post-partum. Pup body weights were recorded on days 1, 4 and 7 post-partum. At the end of the study, macroscopic examination of all F0 males and females and F1 pups was performed. Vehicle: Soybean Oil
Remark	:	This was a range-finding study used to select doses for an embryotoxicity/teratogenicity study and a one-generation study (CIT 8709 RSR). This study is considered reliable as a probe study.
Result	:	No mortalities or treatment-related clinical signs were reported. There was no treatment-related effect on food consumption, body weight gain, mating index, fertility index, mean number of corpora lutea, implantation sites, live fetuses, pre- and post-implantation loss or mean fetal body weight. The gestation index, live birth index, viability indices and mean pup body weights were unaffected by treatment. There were no treatment-related macroscopic changes.
Conclusion	:	Daily administration of epoxidized soybean oil up to 1000 mg/kg bw/day did not induce any toxic effect in parent male or female animals, did not disturb their capacity for reproduction and did not impair development of the F1 offspring.
Reliability	:	(2) valid with restrictions

07.05.2003 (21)

Type	:	other: not specified
Species	:	rat
Sex	:	no data
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	up to 7 weeks
Frequency of treatm.	:	daily
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
No. of generation studies	:	
Doses	:	20% (approximately 10 g/kg bw/day)
Control group	:	no data specified
Method	:	other
Year	:	1963
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	There were no studies of the reproductive ability of these animals.
Result	:	Severe degeneration of the testes.
Test substance	:	ESBO with epoxide numbers 105 or 111.5 The grade of ESBO used in this study does not match the specification of modern commercial ESBO grades.
Reliability	:	(4) not assignable Reliability of 4 assigned because the documentation is insufficient for assessment.

18.05.2004 (5) (6) (34)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Sprague-Dawley
Route of admin.	:	gavage
Exposure period	:	Days 6-15 of gestation
Frequency of treatm.	:	daily
Duration of test	:	To day 20 of pregnancy
Doses	:	100, 300 and 1000 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	> 1000 mg/kg bw
NOAEL teratogen.	:	> 1000 mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	EPOXIDISED SOYBEAN OIL (ESBO) was administered to pregnant female Sprague-Dawley rats during organogenesis (day 6 to day 15 of pregnancy inclusive). Three groups of 25 mated female rats received daily by gavage the test substance at the dose levels of 100, 300 and 1000 mg/kg bw/day, from day 6 to day 15 of pregnancy inclusive. At the beginning of the treatment period, the females were 9 weeks old. The animals were housed individually in polycarbonate cages containing

autoclaved sawdust and equipped with a water bottle. The animals had free access to pelleted diet and water.

Simultaneously, a group of 25 mated females was given the vehicle Soybean oil (SBO) and acted as a control group. The day of mating was designated as day 0 of pregnancy.

Clinical signs including signs of abortion and mortality were checked daily.

The quantity of food consumed was measured for each female at the intervals day 2 - day 6, day 6 - day 9, day 9 - day12, day 12 - day 15 and day 15 - day 20. Food intake per animal and per day was calculated using the difference between the amount of food given and left in each feeder.
Body weight was recorded for each female on days 2, 6, 9, 12,
15 and 20 of pregnancy.
On day 20 of pregnancy, the females were sacrificed, examined macroscopically and fetuses removed by Caesarean section. The litter parameters were recorded: number of corpora lutea, implantation sites, resorptions, dead and live fetuses.
The dams were submitted to a macroscopic examination of the main organs (heart, lung, liver, kidneys, stomach, intestines).
Fetuses were weighed, sexed and submitted to external, soft tissue and skeletal examinations. The soft tissue findings were classified into malformations and anomalies. The skeletal findings were classified into skeletal variations, anomalies and malformations.

Statistical analysis: The mean values were compared by one-way analysis of variances and Dunnett's test. Percentage values were compared by Fisher's exact probability test.

Result : Maternal Data
No clinical signs, no deaths and no abortions were noted in any of the groups. The mean food consumption and body weight gain of the females with completed pregnancy were similar in the control and treated groups. No treatment-related macroscopic changes were observed at necropsy of the females.

Litter data
The mean number of corpora lutea, implantation sites, live fetuses, the post-implantation loss and fetal body weight were similar in the control and treated groups.
The mean number of corpora lutea and implantation sites were similar in the control and treated groups. The pre-implantation loss was higher in each treated group when compared to the control one (23.0%; $p < 0.05$ in the 100 mg/kg/day group - 20.4%; N.S. in the 300 mg/kg/day group 24.4%; $p < 0.01$ in the 1000 mg/kg/day group vs. 16.6% in the control group). The rate of resorptions was similar in the control (2.6%) and the 100 (2.7%), 300 (1.6%) and 1000 (l.1%) mg/kg bw/day groups.

Fetal observations
No external malformations were observed in fetuses of the control or treated groups. No treatment-related soft tissue

anomalies or malformations were noted in fetuses of any group. No dose-related effects were noted on the incidence of the skeletal variations, anomalies or malformations.

SUMMARY OF MATERNAL AND FETAL DATA:

Dose mg/kg/day	0	100	300	1000
Females Alive at Term	23	24	18	20
Dams with viable Fetuses	23	24	18	20
Corpora Lutea (TOTAL)	410	440	323	360
No per animal (MEAN)	17.8	18.3	17.9	18.0
Implantation Sites (TOTAL)	342	339	257	272
Preimplantation Loss				
(TOTAL)	68	101*	66	88**
(%)	16.6	23.0	20.4	24.4
Fetuses (N)	333	330	253	269
No. per animal				
(MEAN)	14.5	13.8	14.1	13.4
(S.D.)	2.0	3.0	1.9	3.7
Live Fetuses (N)	333	330	253	268
No. per animal				
(MEAN)	14.5	13.8	14.1	13.4
(S.D.)	2.0	3.0	1.9	3.7
Resorptions:				
early(N)	6	7	3	3
No. per animal				
(MEAN)	0.3	0.3	0.2	0.2
(S.D.)	0.5	0.6	0.4	0.5
Resorptions:				
late (N)	3	2	1	0
No. per animal				
(MEAN)	0.1	0.1	0.1	0.0
(S.D.)	0.3	0.3	0.2	0.0
Postimplantation los				
(TOTAL)	9	9	4	4
No. per animal				
(MEAN)	0.4	0.4	0.2	0.2
(S.D.)	0.7	0.6	0.4	0.5
Viable Male Fetuses				
(N)	164	176	139	150
(%)	49.2	53.3	54.9	56.0
Female Fetuses (N)	169	154	114	118
(%)	50.8	46.7	45.1	44.0
Fetal Body Weight (g)				
(MEAN)	3.94	4.03	4.02	4.08
(S.D.)	0.23	0.28	0.18	0.39

FETAL ANOMALIES AND MALFORMATIONS
Litters Evaluated
(N) 23 24 18 20
Fetuses Evaluated
(N) 162 160 122 130

ABNORMALITIES:
DILATED RENAL PELVIS
Fetal Incidence
(N) 0 0 3 3
(%) 0.0 0.0 2.5 2.3

Litter Incidence
(N) 0 0 2 3
(%) 0.0 0.0 11.1 15.0

URETER - DILATATION
Fetal Incidence
(N) 0 0 2 1
(%) 0.0 0.0 1.6 0.8

Litter Incidence
(N) 0 0 2 1
(%) 0.0 0.0 11. 5.0

MALFORMATIONS:
VENTRICULAR CEREBRAL DILATATION
Fetal Incidence
(N) 0 0 1 0
(%) 0.0 0.0 0.8 0.0

Litter Incidence
(N) 0 0 1 0
(%) 0.0 0.0 5.6 0.0

Statistical key: * P<0.05 **= P<0.0

Source : Ciba Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
ATOFINA Chemicals

Test substance : Reoplast 39 (oxirane oxygen 6.4%, iodine value 4.3) is 100% Epoxidized Soybean Oil

Conclusion : The test substance EPOXYDISED SOYBEAN OIL (ESBO) when administered daily by oral route (gavage) to pregnant female Sprague-Dawley rats during organogenesis at the dose levels of 100, 300 and 1000 mg/kg bw/day was well tolerated by the dams at all the dose levels and was neither embryotoxic or teratogenic.

Reliability : (1) valid without restriction

Flag : Critical study for SIDS endpoint

03.10.2005 (6) (20)

Species : rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : Treatment began 15 days before mating and up to day 7 post-partum
Frequency of treatm. : daily
Duration of test : Variable, see Remark

Doses	:	150, 450 and 1000 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 1000 mg/kg bw
NOAEL teratogen.	:	= 1000 mg/kg bw
Method	:	other
Year	:	1993
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 12 male and 12 female rats were given up 1000 mg/kg bw/day by gavage. Treatment began 15 days before mating and continued through mating and pregnancy for half the female animals. Treatment continued through lactation and until day 7 post-partum of F1 litters for the other half of the females. Treatment continued for the males through day 7 post-partum. F0 animals were observed daily for clinical signs. Food consumption and body weights were measured at designated intervals. On day 20 of pregnancy, half the females per group were sacrificed, examined macroscopically and fetuses removed by caesarean section. Litter parameters included number of corpora lutea, implantation sites, resorptions, dead and live fetuses. Fetuses were weighed, sexed and examined. The other females were allowed to deliver normally, and F1 litters were examined daily for clinical signs and viability until day 7 post-partum. Pup body weights were recorded on days 1, 4 and 7 post-partum. At the end of the study, macroscopic examination of all F0 males and females and F1 pups was performed. Vehicle: Soybean Oil
Remark	:	This was a range-finding study used to select doses for an embryotoxicity/teratogenicity study and a one-generation study (CIT 8709 RSR). This study is considered reliable as a probe study.
Result	:	No mortalities or treatment-related clinical signs were reported. There was no treatment-related effect on food consumption, body weight gain, mating index, fertility index, mean number of corpora lutea, implantation sites, live fetuses, pre- and post-implantation loss or mean fetal body weight. The gestation index, live birth index, viability indices and mean pup body weights were unaffected by treatment. There were no treatment-related macroscopic changes.
Conclusion	:	Daily administration of epoxidized soybean oil up to 1000 mg/kg bw/day did not induce any toxic effect in parent male or female animals, did not disturb their capacity for reproduction and did not impair development of the F1 offspring.
Reliability	:	(2) valid with restrictions

31.10.2002 (21)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

5.11 ADDITIONAL REMARKS

Type : other: The EU Scientific Committee for Food allocated a temporary TDI (tolerable daily intake) of 1 mg/kg bw for ESBO (maximum oxirane oxygen 8%, maximum iodine value 6)

12.05.2003 (4) (51) (52)

Type : other: The UK COT has recommended a TDI for ESBO of 1 mg/kg bw, derived by applying a 100-fold safety factor to the NOAEL seen in the BIBRA 2-year feeding study in rats.

12.05.2003 (4) (23)

(1) AopWin (v1.90) (2002)

(2) Atofina (2001). Material Safety Data Sheet VIKOFLEX (R) 7170 Epoxidized Soybean Oil. Revision: 4 Issued 05 SEP 2001.

(3) BIOWIN (v4.00) and MITI Model (2002)

(4) British Industrial Biological Research Association (BIBRA) (1986) Project Number 3.0515. Long-Term Study of Epoxidised Soya Bean Oil in the Diet of Rats. Report 515/1/86. Report date October 1986.

(5) British Industrial Biological Research Association (BIBRA) (1988) Toxicology International, Toxicity Profile Epoxidized Soya Bean Oil. PC/BMS/November 1987(g)/P.181/T.1088. Copyright First Edition 1988 by BIBRA.

(6) British Industrial Biological Research Association (BIBRA) (1997) Toxicology International. Toxicity Profile Epoxidised Soya Bean Oil. PW/jab/March 1997 (h)/P.181/T1088/ACN3554.

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(8) Ciba-Geigy (1981a) Unpublished. On the toxicity of epoxidized soya bean oil, Ciba-Geigy Ltd, Basle, Switzerland Project 810818 (cited in BIBRA, 1988; BIBRA, 1997)

(9) Ciba-Geigy (1981b) Unpublished. On the toxicity of epoxidized soya bean oil, Ciba-Geigy Ltd, Basle, Switzerland Project 810819 (cited in BIBRA, 1988; BIBRA, 1997)

(10) Ciba-Geigy (1981c) Unpublished. On the toxicity of epoxidized soya bean oil, Ciba-Geigy Ltd, Basle, Switzerland Project 810820 (cited in BIBRA, 1988; BIBRA, 1997)

(11) Ciba-Geigy (1981d) Unpublished. On the toxicity of epoxidized soya bean oil, Ciba-Geigy Ltd, Basle, Switzerland Project 810062 (cited in BIBRA, 1988; BIBRA, 1997)

(12) Ciba-Geigy (1994). Reoplast 39/TK 11278. Toxicology. Ciba-Geigy Ltd., Additives Division.

(13) CIBA-GEIGY Ltd. (1981) CGL810062, Report on Acute Oral LD50 in the Rat of TK11278, (02/11/81).

(14) CIBA-GEIGY Ltd. (1988) CGL810808, Salmonella/mammalian-microsome mutagenicity test with TK 11278, (08/06/81).

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I U C L I D

Data Set

Existing Chemical	:	ID: 8016-11-3
CAS No.	:	8016-11-3
EINECS Name	:	Linseed oil, epoxidized
EC No.	:	232-401-3

Producer related part

Company	:	Epona Associates, LLC
Creation date	:	28.10.2002

Substance related part

Company	:	Epona Associates, LLC
Creation date	:	28.10.2002
Status	:	
Memo	:	EOD
Printing date	:	12.06.2006
Revision date	:	
Date of last update	:	12.06.2006
Number of pages	:	172
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

Comment : Category Justification

Remark : This category consists of related fatty acid esters. ETP is a monoester with 2-ethylhexanol. EODA is a diester with propylene glycol. ESBO and ELSO are triesters with glycerol (triglycerides). These materials are considered a category for purposes of environmental and health hazard screening assessments because of the similarities metabolism of these materials in microbial, aquatic and mammalian systems. Uptake of any member of this category by microorganisms, aquatic species or mammals is expected to result in quite rapid metabolism by esterases. Carboxylesterases have been demonstrated to be present in many families of fish and aquatic invertebrates as well as mammals (Miller et al., 1981, Sugihara et al., 1994, Escartin and Porte, 1997 and Barron et al., 1999). The action of the esterase will result in a mixture of epoxidized fatty acids and 2-ethylhexanol from ETP, epoxidized fatty acids and propylene glycol from EODA, and epoxidized fatty acids and glycerol from ESBO and ELSO. The similarity of the epoxidized fatty acids which are the primary constituents of the metabolic products of these materials make it possible to use the data of representative materials within this category to assess the potential hazards across the category.

In mammalian species these materials are expected to be absorbed and metabolized in a similar fashion, resulting in the release of similar free epoxidized fatty acids and lesser substituted alcohols or glycerides.

Lipase is an enzyme that assists in the breakdown and digestion of fat in the body. Pancreatic lipase works at the oil/water interface since triglycerides are insoluble. During metabolism in the GI tract, pancreatic lipase preferentially hydrolyzes triglycerides to release the free fatty acids from the SN-1 and SN-3 (terminal) positions of the glycerol backbone. Other products of metabolism are mono- and diglycerides. The monoglycerides, diglycerides, and fatty acids can be absorbed (World Health Organization, 1974)

In a similar manner, pancreatic lipase and other digestive enzymes have been shown to hydrolyze propylene glycol monoesters and diesters in vitro. The absorption,

metabolism and hydrolysis of propylene glycol distearate (which is structurally similar to EODA) were studied in rats using isotopically labelled compounds. These processes for the propylene glycol esters were found to be similar to those of the glycerol esters. So, there is evidence that the propylene glycol esters of fatty acids are hydrolyzed to propylene glycol and fatty acids. (World Health Organization, 1967)

The ETP structure is similar to that of the monoglycerides, formed from the ELSO and ESBO. Further hydrolysis can also occur via carboxylesterase activity.

Hydrolysis data for 61789-01-3 (ETP) is considered to be representative of 68609-92-7 (EODA), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Biodegradation, genetic toxicity, repeated dose, reproductive and developmental data for 61789-01-3 (ETP) and 8013-07-8 (ESBO) are considered to be representative of 68609-92-7 (EODA) and 8016-11-3 (ELSO). The chronic daphnia data for 68609-92-7 (EODA) are considered to be representative of 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO). Acute toxicity data for 61789-01-3 (ETP), 8013-07-8 (ESBO) and 8016-11-3 (ELSO), are considered to be representative of 68609-92-7 (EODA).

06.01.2006 (11) (12)

1.1.0 SUBSTANCE IDENTIFICATION

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	= 100 % w/w
Colour	:	pale yellow
Odour	:	mild

24.11.2003 (6)

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

Adekacizer O 180

06.11.2002

Drapex 10.4

06.11.2002

Epoxidized linseed oil

06.11.2002

Epoxidized linseed oils

06.11.2002

Epoxol 9-5

06.11.2002

Linseed oil, epoxidized

06.11.2002

1.3 IMPURITIES

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 454 - 4536 tonnes produced in 2002

22.09.2005

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : use
Category :

Remark : ELSO is approved for use as an inert ingredient in pesticides. ELSO is primarily used to keep plastics and rubber soft and pliable in flooring, upholstery, food packaging, hoses, tubing, blood bags and other products . The epoxy functionality provides excellent heat and light stability.

06.01.2006 (2) (10)

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	:	= -2.2 °C
Sublimation	:	
Method	:	OECD Guide-line 102 "Melting Point/Melting Range"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	271 K (-21.5 degrees C) +/- 3K
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

28.10.2002 (8)

2.2 BOILING POINT

Decomposition	:	yes
Method	:	OECD Guide-line 103 "Boiling Point/boiling Range"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The test material decomposed from approximately 476 +/- 0.5 K (202.85 degrees C) at 1014.5 kPa without boiling. As the test material decomposed, no value for boiling point could be determined. From data otained in the vapour pressure study (SPL Project number 1666/008), the boiling point of the test material is estimated to be > 633 K at 101.325 kPa.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

19.11.2002 (8)

2.3 DENSITY

Type	:	density
Value	:	1.03 at 20 °C
Method	:	
Year	:	2005
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable Internal company data

18.05.2006 (5)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	< .001 hPa at 25 °C
Decomposition	:	
Method	:	OECD Guide-line 104 "Vapour Pressure Curve"

Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The study was designed in conformance with OECD Guideline 104 to determine vapor pressure using a vapour pressure balance with measurements being made at several temperatures and linear regression analysis to calculate the vapour pressure at 25 degrees C. A sequence of runs was started after a sample of the test material had been under vacuum for approximately 119 3/4 hours. Temperature and pressure readings were taken between 235 and 250 degrees C.
Result	:	No statistical analyses were performed because the balance readings were too low and variable for a line of best fit tohave any meaning. Based on these results, the vapor pressure was determined to be lower than the lowest recommended range for this method or <0.001Pa. On initial degassing, the sample became a clear, extremely pale yellow liquid. The test material did not further change in appearance under the conditions used in the determination.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

07.05.2003 (9)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	
Log pow	:	> 6.2 at °C
pH value	:	
Method	:	OECD Guide-line 117 "Partition Coefficient (n-octanol/water), HPLC Method"
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The standard used was DDT. The pH of the mobile phase was adjusted to 3 to assure that the test substance was tested in non-ionized form.
Result	:	The partition coefficient of the test material has been determined to be > 1.59 x 10+6, Log 10 Pow > 6.2
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

19.11.2002 (8)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	= .00094 g/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	

Method	:	OECD Guide-line 105
Year	:	2002
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is the nature of these EOD materials to form an emulsion upon mixing in water. They do not dissolve and they do not remain as individual molecules in solution, which reflects the difficulty with which the undissolved microemulsion is separated from true aqueous solution. This was confirmed in the attempts to prepare appropriate water accommodated fractions (WAF) of EODA (CAS number 68609-92-7), which did not contain dissolved test substance at or above the method detection limit of 0.05 mg/L. These results from the WAF preparation suggest that actual water solubility of the EOD substances are lower than reported above.
Result	:	The test material forms a turbid emulsion upon mixing in water. Each sample, on completion of centrifugation, was isolated as a clear colourless soluton prior to analysis. However significant variance between sample concentrations was obtained on analysis of definitive test 1. Therefore an additional determination, definitive test 2, was carried out at a reduced loading concentration. This was performed in an attempt to minimize emulsification and therefore aid sample clean up and thus sample consistency. However, again the sample results represented a significant range of concentrations. Therefore it was concluded that although each solution appeared clear and colourless prior to analysis, due to the behaviour of the test material in water, removal of all excess undissolved material may not have been complete. A final determination was performed with the inclusion of a filtration step, using a 0.2 um membrane, during sample clean up. Although no detectable concentrations of test material were found in solution on analysis, this determination was shown to be invalid and is not presented. During post-analysis validation of filtered procedural recoveries, the test material was found to have a strong adsorption affinity for the filters. The preliminary water solubility test indicated that the column elution method should have been performed as the solubility was less than 1 x 10-2 g/l. However, due to the physical nature of the test material, it was not possible to use this method. Experience has shown that coating of liquid test materials onto glass beads causes them to adhere together, forming a plug within the column which prevents water circulation. The water solubility of the test material was determined to be 9.37 x 10-4 g/l at 20.0 +/- 0.5 deg C, which represents the mean for six mixtures exhibiting solubilities over the range 4.21 x 10-4 to 1.78 x 10-3 g/l.
Reliability	:	(1) valid without restriction
Flag	:	Critical study for SIDS endpoint

12.06.2006 (8)

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

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 2.2 hour(s)
Degradation	:	% after
Quantum yield	:	
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	
Rate constant	:	= .0000000000579673 cm³/(molecule*sec)
Degradation	:	% after
Deg. product	:	
Method	:	other (calculated): AopWIN (v1.90)
Year	:	2002
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Atmospheric Oxidation (25 deg C) [AopWin v1.90]: Hydroxyl Radicals Reaction: OVERALL OH Rate Constant = 57.9673 E-12 cm3/molecule-sec Half-Life = 0.185 Days (12-hr day; 1.5E6 OH/cm3) Half-Life = 2.214 Hrs
Test substance	:	SMILES code = C(OC(=O)CCCCCCCC5OC5CC6OC6CC7OC7CC)C(OC(=O)CCCCCCCC4OC4CCCCCCC)C(OC(=O)CCCCCCCC1OC1CC2OC2CC3OC3CC)
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

18.05.2004 (1)

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

Type	:	fugacity model level III
Media	:	
Air	:	% (Fugacity Model Level I)
Water	:	% (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: EPIWIN (v3.05)

Year : 2002

Result : Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	5.14e-026	4.54	0
Water	1.28	3.6e+003	1000
Soil	31.6	3.6e+003	1000
Sediment	67.1	1.44e+004	0

Persistence Time: 8.21e+003 hr hr

Test substance : SMILES code =
C(OC(=O)CCCCCCCC5OC5CC6OC6CC7OC7CC)C(OC(=O)CCCCCCCC
4OC4CCCCC
CC)C(OC(=O)CCCCCCCC1OC1CC2OC2CC3OC3CC)

Molecular Wt: 975.37
Henry's LC : 4.52e-021 atm-m3/mole (Henrywin program)
Vapor Press : 1.08e-022 mm Hg (Mpbpwin program)
Liquid VP : 1.76e-019 mm Hg (super-cooled)
Melting Pt : 350 deg C (Mpbpwin program)
Log Kow : 6.2 (user-entered)
Soil Koc : 6.5e+005 (calc by model)

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
18.05.2006 (7)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Deg. product :
Method : other: modeling
Year : 2002
GLP :
Test substance : as prescribed by 1.1 - 1.4

Result : Probability of Rapid Biodegradation (BIOWIN v4.00):
Linear Model : -1.5240
Non-Linear Model : 0.0000
Expert Survey Biodegradation Results:
Ultimate Survey Model: 1.6710 (recalcitrant)
Primary Survey Model : 3.3081 (days-weeks)
Readily Biodegradable Probability (MITI Model):
Linear Model : 0.7139
Non-Linear Model : 0.0029

Test substance : SMILES =
C(OC(=O)CCCCCCCC5OC5CC6OC6CC7OC7CC)C(OC(=O)CCCCCCCC
4OC4CCCCC
CC)C(OC(=O)CCCCCCCC1OC1CC2OC2CC3OC3CC)

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
18.05.2004 (3)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

Elimination :
Method : other
Year : 2002
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Remark : Taken alone, the estimated log Kow > 6.2 indicates a high potential for bioaccumulation according the TGD. Using the non-linear QSAR recommended for substances having log Kow > 6, a log BCF value of 4.6 is estimated. However, substances having molecular weight > 700 Daltons are considered to have low bioaccumulation potential, due to steric hindrance of membrane permeation.
If taken up into fish, these fatty acid ester substances are expected to be rapidly metabolized and excreted. Due to their demonstrated potential for rapid metabolism in fish, the category of linear aliphatic fatty acid esters have recently been categorized by Environment Canada as having low potential to bioaccumulate.

Result : BCF Program (v2.15) Results:
==========
SMILES :
C(OC(=O)CCCCCCCC2OC2CC1OC1CCCCC)C(OC(=O)CCCCCCCC3O
C3CCCCCCCC)(OC(=O)C
CCCCCCCCCCCCCCCC)
CHEM :
MOL FOR: C56 H102 O9
MOL WT : 919.43

Bcfwin v2.15 ----------
Log Kow (estimated) : 18.90
Log Kow (experimental): not available from database
Log Kow used by BCF estimates: 6.20 (user entered)

Equation Used to Make BCF estimate:
Log BCF = 0.77 log Kow - 0.70 + Correction

Correction(s): Value
Alkyl chains (8+ -CH2- groups) -1.500

Estimated Log BCF = 2.574 (BCF = 375)

Reliability : (2) valid with restrictions
Modeled data

30.05.2006 (7)

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	:	= 14.9 ml/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	male
Number of animals	:	20
Vehicle	:	other: dosed as received
Doses	:	
Method	:	
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : Compounds were administered by stomach intubation to Wistar derived male rats, 90-120 grams in weight and 3 to 4 weeks of age. The nonfasted rats were maintained on appropriate Wayne diets and water ad lib except during period of manipulation or confinement.

Dosage levels differ by a factor of 2 in a geometric series. Dosage levels administered in this study: 32.0, 16.0, 8.0, and 4.0 ml/kg.

The LD50 was calculated by the moving average method based on a 14-day observation period.

Remark : Although the study title implies this was a range-finding study, this was a definitive study and no further testing was necessary.

Result : Dosage: 32.0 ml/kg
Dead/Dosed: 5/5
Days to Death: 0, 1, 2, 2, 4
Weight Change: -
Signs and/or Symptoms: Sluggish, pilo-erection 3 hr; diarrhea, fur around mouth blood-stained 1 day; pilo-erection, blood on nose 2 days; death of 1 in 5.5 hr

Dosage: 16.0 ml/kg
Dead/Dosed: 3/5
Days to Death 0, 1, 1
Weight Change: 101 to 130 gm
Signs and/or Symptoms: Clonic convulsions 7 hr; death of 1 in 5 hr; fur yellow 1 day.

Dosage: 8.0 ml/kg
Dead/Dosed: 0/5
Days to Death: -
Weight Change: 127 to 136 gm
Signs and/or Symptoms: Fur stained yellow 1 day.

Dosage: 4.0 ml/kg
Dead/Dosed: 0/5
Days to Death: -
Weight Change: 106 to 136 gm

Signs and/or Symptoms: Fur yellow 1 day (2 rats).

Gross Pathology: In victims, petechial hemorrhages of the lungs; livers pale, mottled, burned; spleens mottled; kidneys pale and sections congested; adrenals congested; stomachs distended, gas-filled; pylori pink; intestines distended, gas or liquid-filled, yellow and pink in sections. In survivors, petechial hemorrhages of the lungs; acini of livers prominent; kidneys speckled, sections congested; intestines gas -filled; adrenals slightly congested.

LD50 = 14.9 (10.3 to 21.6) ml/kg

Test substance : Flexol Plascticizer LOE is 100% Epoxidized Linseed Oil
Conclusion : Slightly toxic following acute peroral intubation.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
12.05.2003 (4)

5.1.2 ACUTE INHALATION TOXICITY

Type :
Value :
Species : rat
Strain :
Sex : no data
Number of animals : 6
Vehicle :
Doses :
Exposure time : 8 hour(s)
Method :
Year : 1977
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : Static exposure at 26 degrees C. Substantially saturated vapor was prepared by spreading 50 grams of chemical over 200 cm2 area on shallow tray placed near the top of a 120-liter glass chamber which was then sealed for at least 16 hours while an intermittently operated fan agitates the internal chamber atmosphere. Rats were then introduced in a gasketed drawer-type cage designed and operated to minimize vapor loss. The nonfasted animals were maintained on appropriate Wayne diets and water ad lib except during period of manipulation and confinement.
Remark : Although the study title implies this was a range-finding study, this was a definitive study and no further testing was necessary.
Result : Concentration: Substantially saturated vapor.
Dead/Dosed: 0/6
Death: -
Weight Change: 45 to 71 gm
Signs and/or Symptoms: -

Gross Pathology: Nothing remarkable
Test substance : Flexol Plascticizer LOE is 100 % Epoxidized Linseed Oil
Conclusion : No hazard in anticipated from the infrequent inhalation of substantially saturated vapor evolved at room temperature under normal handling conditions.

Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meet important criteria of today's standard methods.

12.05.2003 (4)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 16 - ml/kg bw
Species	:	rabbit
Strain	:	other:albino
Sex	:	male
Number of animals	:	7
Vehicle	:	other: dosed as received
Doses	:	
Method	:	
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Male albino rabbits, 3 to 5 months of age, were immobilized during the 24-hour contact period with the compound retained under impervious sheeting on the clipped intact skin of the trunk. Thereafter, excess fluid was removed to prevent ingestion. Maximum dosage that can be retained is 16 to 20 ml/kg. A dosage of 16.0 ml/kg was evaluated in this study. The nonfasted animals were maintained on appropriate Wayne diets and water ad lib except during period of manipulation or confinement.
Remark	:	Although the study title implies this was a range-finding study, this was a definitive study and no further testing was necessary.
Result	:	Dosage: 16.0 ml/kg Dead/Dosed: 1/7 Days to Death: 3 Weight Change: 62, 155, 216, 227, 273, 290 gm Skin Irritation: erythema Signs and/or Symptoms: diarrhea in victim at time of death Gross Pathology: In victim, kidneys pale. In survivors, kidneys mottled.
Test substance	:	Flexol Plascticizer LOE is 100% Epoxidized Linseed Oil
Conclusion	:	Extremely low order of acute toxicity following covered dermal application.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

12.05.2003 (4)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Open
Exposure time	:	24 hour(s)
Number of animals	:	5
Vehicle	:	

PDII	:	
Result	:	not irritating
Classification	:	
Method	:	
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Chemical was applied in 0.01 ml amounts to clipped, uncovered intact skin of 5 rabbit bellies undiluted. In the grading scale used in the study ten grades are recognized based on appearance of moderate or marked capillary injection, erythema, edema or necrosis within 24 hours. No injury from undiluted = Grade 1. The nonfasted animals were maintained on appropriate Wayne diets and water ad lib except during period of manipulation or confinement.
Remark	:	Although the study title implies this was a range-finding study, this was a definitive study and no further testing was necessary.
Result	:	No irritation on 5 rabbits. Grade 1.
Test substance	:	Flexol Plascticizer LOE is 100% Epoxidized Linseed Oil
Reliability	:	(3) invalid Reliability of 3 assigned because the study does not meet important criteria of today's standard methods (only applied 0.01 ml).

18.05.2004 (4)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.5 ml
Exposure time	:	24 hour(s)
Comment	:	
Number of animals	:	5
Vehicle	:	
Result	:	not irritating
Classification	:	
Method	:	
Year	:	1977
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Eyes not staining with 5% fluorescein in 20 seconds contact were accepted. Single instillation of 0.5 ml undiluted chemical was made into the conjunctival sac of 5 rabbits. Read immediately unstained and after fluroescein at 24 hours, with ten grades recognized. Trace or no injury from 0.5 ml undiluted = Grade 1. The nonfasted animals were maintained on appropriate Wayne diets and water ad lib except during period of manipulation or confinement.
Remark	:	Although the study title implies this was a range-finding study, this was a definitive study and no further testing was necessary.
Result	:	No corneal injury on 5 eyes from an excess, 0.5 ml per eye. Grade 1.
Test substance	:	Flexol Plascticizer LOE is 100% Epoxidized Linseed Oil
Reliability	:	(2) valid with restrictions

05.08.2005 (4)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

5.5 GENETIC TOXICITY 'IN VITRO'

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

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

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