SIDS Initial Assessment Report

For

SIAM 17

Arona, Italy,11-14 November 2003

1.	**Chemical Name:**	Di(2-ethylhexyl)terephthalate (DEHT)
2.	**CAS Number:**	6422-86-2
3.	**Sponsor Country:**	USA U.S. Environmental Protection Agency Mr. Oscar Hernandez, Director Risk Assessment Division (7403M) 1200 Pennsylvania Ave., NW Washington, DC 20460 Phone: 202-564-7641
4.	**Shared Partnership with:**	No partner, single sponsor
5.	**Roles/Responsibilities of the Partners:**	Not applicable
•	Name of industry sponsor /consortium	Eastman Chemical Company
•	Process used	Eastman Chemical Company conducted a comprehensive literature search, including all generally accepted databases, reference books, unpublished studies and data in company files. This information formed the basis for compilation of the IUCLID dossier.
6.	**Sponsorship History**	
•	How was the chemical or category brought into the OECD HPV Chemicals Programme?	Eastman Chemical Company agreed to sponsor DEHT in the ICCA program, with the U.S. EPA being the country sponsor.
7.	**Review Process Prior to the SIAM:**	SIDS Dossier and Testing Plan were reviewed by the US EPA and the following SIDS Testing Plan was recommended: no testing (X) testing ( )
8.	**Quality check process:**	On completing the literature search and data collection, important and significant studies were identified for all endpoints. These studies were reviewed and summarized

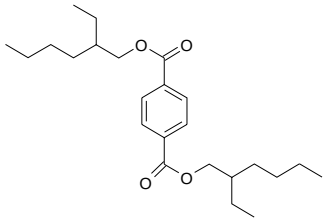
following current guidelines for robust summaries. Reliability ratings were assigned following the Klimisch rating system. The key studies were identified based on completeness, protocol and GLP use and other quality factors. These were flagged as critical studies. The summaries were compiled using the IUCLID program.

9. Date of Submission: August 2003

10. Date of last Update: October 2003

11. Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	6422-86-2
Chemical Name	Di(2-ethylhexyl)terephthalate (DEHT)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Di(2-ethylhexyl)terephthalate (DEHT) has been shown in both *in vitro* and *in vivo* studies to have the potential to undergo complete hydrolysis to yield terephthalic acid and 2-ethylhexanol (2-EH), which are rapidly eliminated. Results of these metabolism studies also indicate DEHT was not well absorbed within the gastrointestinal tract, with 36% of it recovered in the feces still intact. In addition, a study to assess dermal absorption rate indicated that DEHT has a very low potential to penetrate the skin (0.103 μg/cm^2/hr), which further limits systemic exposure potential.

The acute oral LD_{50} values are in excess of 3,200 mg/kg in mice and 5,000 mg/kg in rats. The acute dermal LD_{50} value is in excess of 19,670 mg/kg bw in guinea pigs, and skin and eye irritation studies in animals and/or humans indicate that DEHT has only a slight potential to induce irritation. In studies with some limitations, no skin sensitization was observed in humans or animals.

In one repeated dose study, rats were fed diets containing up to 2.5% (approx. 2,000 mg/kg bw/day) DEHT for 21 days, while in the other they received up to 1% DEHT in the diet for 90 days (approx. 561 mg/kg bw/day for males and 617 mg/kg bw/day for females). The NOELs in both studies were 0.5 % (approximately 500 mg/kg bw/day in the 21 day study and 277 – 309 mg/kg bw/day in the 90 day study). The only effect noted at 1.0 % in the 90 day study was increased relative liver weight. In the 21-day study, administration of 1.0 % was associated with increased relative liver weight in females but was without effect in males. Peroxisome proliferation in the liver was not noted in animals treated with either of these dosing regimens.

DEHT has been shown to be negative in both mutagenicity and chromosomal aberration assays with and without metabolic activation. No carcinogenicity data are available.

The reproductive toxicity of DEHT has been assessed through a two-generation study in rats following OECD Test Guideline 416. The NOAEL for reproductive toxicity was 1.0% in the diet (500-700 mg/kg bw/day for males and 800-1000 mg/kg bw/day for females; highest dose tested), and the NOAEL for parental and offspring toxicity based on reduced body weight gains was 0.3% (150-200 mg/kg bw/day for males and 250-300 mg/kg bw/day for females).

Mean maternal body weights and body weight gains were reduced for F0 and F1 females in the 1.0% group throughout pregnancy and decreased mean terminal body weights were noted in F1 males and females given 0.6% or 1.0% test material. The results of this study, in conjunction with the 90-day study described above which also showed no effect of DEHT on histology of reproductive organs indicate that DEHT has a low potential to induce reproductive toxicity.

Developmental toxicity was evaluated in a dietary study following OECD Test Guideline 414. The NOEL for maternal toxicity was 0.6% (458 mg/kg/day) and the NOEL for developmental toxicity was 1.0% (747 mg/kg/day; highest dose tested). The ability of DEHT to induce anti-androgenic like effects in male offspring was assessed by giving pregnant rats 750 mg/kg DEHT by gavage on gestation day 14 until postnatal day (PND) 3. No changes indicative of a feminization effect were induced in male pups. Results of a uterotrophic assay in which immature females were given up to 2000 mg/kg/day DEHT by gavage on PND 19-21 also indicate that DEHT does not possesses estrogenic activity.

Environment

DEHT is a high boiling liquid (boiling point 383°C at 1015 hPa) with a very low vapour pressure (estimated to be 2.85 E-5 hPa at 25°C by EPIWIN). It has a melting point of -48°C, a water solubility of 0.0004 mg/l and an EPIWIN-estimated octanol/water partition coefficient of 8.39. The atmospheric photodegradation half-life is 0.487 days (5.84 daylight hours). Based on its molecular structure, DEHT is not anticipated to undergo rapid hydrolysis in the presence of water. Level III fugacity modeling assuming equal distribution indicates 0.743% to air, and 7.26% to water with greater percentages in the soil and sediment compartments (28% and 64%, respectively). These results are supported by a Koc value of 1.62 E+5. While the vapour pressure of DEHT is very low, the Henry's Law Constant is relatively high (1.02 E-5 atm-m^3/mol) due to the substance's offsetting low aqueous solubility. A biodegradation study failed to show that the material was "readily biodegradable" under the method and conditions of the test, but did show 40.2% conversion to CO2 in 28 days indicating that the material is ultimately biodegradable. Results of an activated sludge respiration inhibition test indicate that DEHT is not toxic to wastewater microbes. Studies assessing acute and chronic toxicity to fish (Fathead minnow and Rainbow trout) and invertebrates (*Daphnia magna*, Planorbid snail, Eastern oyster), and acute affects on algal (*Selenastrum capricornutum*) growth showed no effects at water concentrations that were often significantly greater than its limit of solubility in distilled, deionized water that is free of particulate matter (0.0004 mg/L). Terrestrial plant growth in three species was not affected by DEHT exposure. An OECD sediment-water chironomid toxicity test using spiked sediments indicated that the EC50 was greater than the highest concentration recommended by the method (1000 mg/kg nominal, 950 mg/kg measured) and the NOEC was 180 mg/kg. A bioconcentration study in oysters indicated that the material has a medium to low potential to bioconcentrate (BCF = 393). However, due to its propensity to be eliminated by higher trophic organisms, it is not expected to bioaccumulate.

Exposure

A single U.S. manufacturer produces DEHT using a continuous reactor, distillation column and storage tanks. Annual production is about 25-50 thousand metric tons. Occupational exposure is limited by the closed process, and also because the substance is a high boiling liquid of limited volatility. The primary use of DEHT is as a plasticizer whereby it is bound

in a polymer matrix, limiting consumer exposure. Some consumer exposure may occur based on a minor use in coated fabrics, but the application is on the exterior of the fabric, away from direct dermal contact, and the DEHT is bound up in the polymer. Concentrations of DEHT in the environment in air or water have not been reported, but there is limited potential for release into the environment. Environmental releases during manufacture and processing are limited by the use of enclosed processes and by in-plant treatment of any waste streams through biodegradative waste treatment or incineration. DEHT is released slowly into the environment from various uses of PVC, such as in PVC waterstops, gaskets, weather stripping, shoe soles, pond linings and wire coatings. Any DEHT that may enter the environment will have a strong tendency to be adsorbed onto solid matter such as soil and sediment.

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

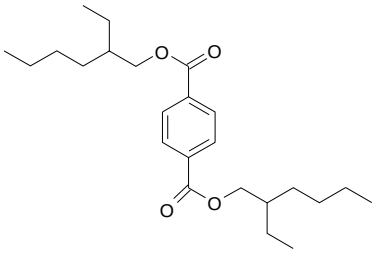
The chemical is currently of low priority for further work because of its low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 6422-86-2
IUPAC Name:
Molecular Formula: C24 H38 O4
Structural Formula:



Molecular Weight: 390.57
Synonyms: 1,4-benzene dicarboxylic acid, di-2-ethyhexyl ester; Dioctyl Terephthalate (DOTP); Di-(2-ethylhexyl) Terephthalate (DEHT); Eastman® 168 Plasticizer

1.2 Purity/Impurities/Additives

DEHT is a clear liquid at room temperature and is manufactured at >98% purity. Minor impurities (present at <2%) include 2-ethylhexyl methyl terephthalate (CAS Registry No.: 63468-13-3).

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Method/Reference
Physical state	clear liquid	
Melting point	-48°C	Unknown / Beeler, 1976
Boiling point	383° C at 1015 hPa	Unknown / Beeler, 1976
Relative density	0.984 g/cm^3 @ 20°C*	Unknown / Eastman Chemical Co.
Vapour pressure	1013 hPa at 398°C 0 hPa at 25 °C 2.85 E-5 hPa at 25°C	Measured / Eastman Chemical Co. Calculated / Eastman Chemical Co. Estimation / EPIWIN
Water solubility	0.0004 mg/l at 22.5°C	"Slow-stir" method; Eastman Chemical Co.
Partition coefficient n-octanol/water (log value)	8.39	EPIWIN Kowwin (v1.66)
Henry's law constant	1.18 E-5 atm-m^3/mol	Estimation / EPIWIN Henry (v3.10, Bond method)

* Study was given a reliability rating of 4 because data were obtained from a secondary source

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Manufacture

Bis(2-ethylhexyl)terephthalate or di(2-ethylhexyl)terephthalate (DEHT) is manufactured in the US by one producer by combining terephthalic acid with 2-ethylhexanol. Manufacture takes place in a closed, continuous process. The manufacturing equipment includes a reactor column for continuous manufacture, a distillation column and one or more storage tanks, with related lines and instrumentation and vents and scrubbers. The substance is purified by distillation in the closed continuous distillation column. U.S. Production levels of 25-50 thousand metric tons were reported for 1998 (US EPA, 1988). Eastman Chemical Company is the only known manufacturer and is located in the United States. Therefore, global production is estimated to be the same as U.S. Production.

In the U. S., DEHT is not listed as a Toxic Release Inventory (TRI) chemical under EPCRA 313, or as a Hazardous Air Pollutant.

Uses

DEHT is used primarily as a plasticizer for PVC in applications where low volatility, low migration, and flexibility at low temperatures are desired. These applications include wire and cable coatings, pond liners, shoe soles, gaskets used for bottle caps and enclosures, flooring products and weather-stripping. There is some use in coated fabrics to make them water proof. There is no known current use in medical devices.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Limited potential exists for major releases to the environment during manufacture, since a closed system is used during production by a single global manufacturer. Organic waste streams from the process are incinerated, and any aqueous waste stream is treated on the plant site in a fully qualified and registered biological waste water treatment system. The material is stored in a tank at the producer's site, and is transported to users in rail cars, tank trucks, or drums. Less than 2% of total production is drummed. Although storage and transport in drums offers a different potential for exposure and possible spills (as compared to that for tank cars and trucks), exposure potential is still limited. Drums used are typically 55-gallon stainless steel with drum openings of no more than 2.5 inches in diameter. Filling and emptying of drums is conducted using closed lines placed in the opening. Drumming is usually done out-of-doors, which provides open ventilation. The time required for filling or emptying each drum is less than five minutes. All of these factors, especially considering the very low vapour pressure of DEHT, limit exposure during drumming operations.

The primary use of DEHT is as a plasticizer, formulated into plastic matrixes (typically at levels of 15% or less). Little or no wastes are generated in the formulation step, which is simply mixing DEHT with the plastic components in a closed reactor. The largest potential for environmental release of DEHT is as a component bound up in spent or recycled plastic, or from slow gradual release from plastics. However, the driving force for this to occur is not anticipated to be significant due to its extremely low water solubility and vapour pressure. In addition, plastics in landfills remain essentially intact in the absence of sunlight.

Information on measured environmental concentrations of DEHT is unavailable. Physical properties and environmental fate and transport data discussed below indicate that DEHT, if released to the environment, will adhere strongly to soil or sediment, but will not easily enter or persist in the atmospheric or aqueous compartments, based on very low water solubility and very low vapour pressure. The potential for spreading DEHT in sewage sludge from municipal sewage treatment plants should be low because free DEHT is not expected to enter municipal sewage plants.

2.2.2 Photodegradation

The rate constant 21.9554 E-12 cm^3/molecule-sec was estimated using AOP (v1.90) for hydroxyl radical induced photodegradation (EPIWIN v3.10). The corresponding half-life ($T_{1/2}$) is 0.487 days (5.846 hours in 12 hrs of daylight), which indicates it would be rapidly degraded in the atmosphere. It should be pointed out that atmospheric photodegradation is not expected to be an important degradative pathway, since DEHT has low potential to enter the atmosphere based on its extremely limited volatility.

2.2.3 Stability in Water

The EPIWIN HYDROWIN Program (v1.67) calculates a hydrolysis half-life at pH 7 of > 1 year at ambient temperatures, based on molecular fragment analysis. This program is limited for DEHT in that the program does not have a complete library for all molecular fragments for this substance. DEHT contains two ester groups, which would be the primary sites subject to hydrolysis. Hydrolysis of most esters occurs slowly under neutral, ambient conditions, but is enhanced by the presence of strong base and elevated temperatures. The extremely limited water solubility of DEHT further reduces the likelihood of rapid hydrolysis in the environment.

2.2.4 Transport between Environmental Compartments

The environmental distribution of DEHT is determined by its water solubility, water sediment and water-soil distribution coefficients, and partitioning between air and water. Fugacity Level III modelling has been conducted for DEHT using EPIWIN, with measured values for melting point, boiling point, and water solubility used as inputs to the program. Also inputted to the model were emissions of 1000 kg/hr to each of air, water and soil compartments. Otherwise, defaults estimated by the EPIWIN model were used. This model indicates that limited amounts would partition to air (0.743%) and water (7.26%), with greater percentages occupying the soil (28%) and sediment (64%) compartments. This model also estimates the half-life of the compound in each compartment. The half-life estimates for DEHT are air = 12 hours, water = 360 hours, soil = 360 hours and sediment = 1.4 x 10^3 hours. The half-life estimates, especially for water, soil and sediment may have limited reliability, since the BIOWIN program (v4.00) predicts that DEHT biodegrades readily, in contrast with available measured data that indicate biodegradation takes place more slowly. Overall, the persistence time of DEHT in the environment is estimated to be 448 hours. The very low vapour pressure (estimated to be 2.85 E-5 hPa at 25ºC) and water solubility (0.0004 mg/l) are further indicative that soil and sediment are the preferred compartments. A Henry's Law Constant of 1.02 E-5 atm-m^3/mol was estimated (HENRY v3.10). While the vapour pressure of DEHT is very low, the Henry's Law Constant is relatively high due to the substance's offsetting low aqueous solubility. A soil/sediment partition constant (Koc) was estimated using PCKOCWIN (v1.66) with the above inputs (EPIWIN v3.10). The value of 1.62 E+5 indicates that DEHT would adhere strongly to soil and sediment particles and have limited mobility in soil.

2.2.5 Biodegradation

Biodegradation of DEHT was studied following the EPA Aerobic Biodegradation Guideline (Analytical Bio-Chemistry Laboratories, Inc., 1985a). Both primary and ultimate biodegradability were measured using 14C-labeled DEHT. The sample of ^{14}C-DEHT used in the study contained a ^{14}C tag in the 2-ethylhexyl side chain. The test plan consisted of a 2-week acclimation period followed by a 28-day biodegradation study using 1 mg-C/L of DEHT. Radioanalysis indicated that 40.2% of DEHT was converted to CO_2 and gas chromatographic measurements showed that 56.2% of the DEHT was lost from the medium. The results of the CO_2 trapping analysis indicate that the half-life for ultimate biodegradation to CO_2 was greater than 28 days, and results of the gas chromatographic analysis indicate a half-life of less than 28 days for primary biodegradation. The study showed that DEHT is ultimately biodegradable, but not "readily biodegradable". The results of this study may have been influenced by the very low water solubility of DEHT and its partitioning onto the surfaces of the test vessel and inoculum.

The potential of spreading DEHT in sewage sludge from municipal sewage treatment plants should be low because free DEHT is not expected to enter municipal sewage plants. Algorithms are also available in EPIWIN to estimate the fate of a compound during secondary (aerobic) wastewater treatment. For DEHT, the most significant pathway during treatment is sludge adsorption due to its very large partitioning coefficients (Kow and Koc). Estimates of the relative pathways are: total removal = 94.0%, total biodegradation = 0.78%, total sludge adsorption = 93.25%, and total emission to air = 0%. Any DEHT present in the treatment plant effluent is likely to be sorbed to particulates and suspended materials.

A 3-hour activated sludge respiration inhibition test was performed using activated sludge from a domestic wastewater treatment plant (Moulton, 2003). The sludge microorganisms were exposed to five concentrations of the test substance. The respiration rate, expressed as oxygen consumption by the microbes in mg O_2 per liter per hour, was measured under defined conditions following the 3-hour exposure period. Inhibition values were calculated by comparing test respiration rates to negative control rates. The 3-hour respiration inhibition test resulted in an EC_{50} value >10 mg/l and a NOEC of 10 mg/l, the highest concentration tested. Thus, DEHT is not expected to inhibit respiration of secondary wastewater treatment microorganisms.

To remove in section 4.3 other effects

2.2.6 Bioaccumulation

The BCFWIN program (version 2.14) inputted with measured values for melting point, boiling point and water solubility predicts a bioconcentration factor (BCF) of 25.31. A mean BCF of 393 was determined based on the results of a 24-day study conducted in oysters following a prescribed EPA protocol (Battelle, 1986a)(See section 4.3 for details). Following the exposure period there was a 70% reduction of the measured test substance in the oyster soft tissue after a 14-day depuration period. Although DEHT does have a low to medium potential to accumulate in the aquatic food web, it is not expected to biomagnify because of its propensity to be eliminated by organisms.

2.3 Human Exposure

2.3.1 Occupational Exposure

Workplace exposure to DEHT during manufacture is minimized by the use of enclosed equipment, engineering controls, the low volatility of the substance and through the use of good industrial

hygiene practices, which include personal protective equipment such as gloves and a dust mask as appropriate. Based on a single US producer, it is estimated that no more than 25 individuals in the USA are involved in the manufacturing and handling process, with a maximum duration of exposure of 140 hours per worker per year.

The primary use of DEHT is as a plasticizer where it is bound up in a polymer matrix. Although exposure by employees to DEHT during processing into final products has not been quantified, exposure is likely minimized through the use of enclosed equipment and by good industrial hygiene practices. Processing is done in both closed and open equipment. In both closed and open equipment, exposure is minimized by the use of localized exhaust and subsequent catalytic incineration or aerosol capture of any DEHT volatilized from the polymer matrix.

Exposure to vapours is unlikely because the vapour pressure for DEHT is low (estimated to be 2.85 E-5 hPa at 25 °C) unless it is heated where (at the lowest measured temperature of 270 °C the vapour pressure was still only 13.3 hPa). According to the US DEHT producer, incorporation of DEHT into products does not require heating to a temperature greater than 149°C (300°F). Exposure to an aerosol is unlikely during loading for storage and transport, and the likelihood of significant inhalation or dermal exposure is further reduced through the use of good industrial hygiene practices (i.e. personal protective equipment such as gloves and a dust mask if the worker deems it appropriate).

2.3.2 Consumer Exposure

Exposure by consumers has not been quantified, but is considered to be minimal based on the very limited use of DEHT in consumer products. Furthermore, exposure is primarily limited to the dermal route. Systemic exposure by the dermal route is significantly attenuated, as shown by the fact that DEHT has an extremely low percutaneous absorption rate (0.103 ± 0.052 $\mu g/cm^2/hr$). The only consumer product that creates a potential for direct dermal exposure is “coated fabrics”. These fabrics have a flexible vinyl coating applied to them in order to make them waterproof. Importantly, the coating is applied to only a single side of the fabric (i.e., the outside), thus significantly limiting the amount of dermal contact that may occur. In the case of waterproof fabrics for hospital beds, the vinyl-coated side is located directly against the mattress. This is followed by the placement of a conventional cotton sheet over the top of the non-coated side, further reducing a patient’s potential exposure to the vinyl coating. Typically, the vinyl coating on such fabric contains 23-26% DEHT.

Some human exposure to DEHT may occur as a result of the presence of this substance in the environment. As discussed above, concentrations of DEHT in the environment have not been reported, but air and water concentrations are expected to be low based on very limited vapour pressure and water solubility. Most DEHT entering the environment will be adsorbed onto solid matter such as soil and sediment.

3 HUMAN HEALTH HAZARDS

Table 2 below provides a tabular results summary for the mammalian toxicology endpoints.

Table 2 Summary of Mammalian Toxicity

Endpoint	Method	Result/NOEL (NOAEL)[1]	Reference
Acute Toxicity (LD_{50})	Other: oral, rodent	>5,000 mg/kg (rats) >3,200 mg/kg (mice)	Shepard, 1994 Gordon, 1975
	Other: dermal, guinea pig,	>19,670 mg/kg	Gordon, 1975
Irritation	Other: eye, rabbit	Slight	Gordon, 1975
	Other: dermal, guinea pig and human	Slight	Gordon, 1975 Lockhart, 2001a
Sensitization	Other: foot-pad, guinea pig	Negative	Sharp, 1975
	Other: Modified Draize – HRIPT; human	Negative	Lockhart, 2001b
Repeated Dose Toxicity	Other: Similar to USEPA 799.9310, 90 days, diet (0.1, 0.5, 1.0%), rat	0.5% (277-309 mg/kg/d)	Barber and Topping, 1995
	Other: 21 days, diet (0.1, 0.5, 1.0, 1.2, 2.5%), rats	0.5 % (487-505 mg/kg/d)	Topping, 1987
	Other: 10 days, diet (0.1 and 1.0%), rats	1.0% (885 mg/kg/d)	Gordon, 1986
	Other: 10 days, inhalation (46 mg/m^3, only conc.), rat	46 mg/m^3	Gordon, 1986
Genotoxicity – Mutation	Ames (Similar to OECD 471) with *Salmonella* strains TA1535, TA1537, TA1538, TA98, and TA100	Negative	Barber, 1994a
	HGPRT assay (Similar to OECD 476), with Chinese hamster ovary (CHO) cells	Negative	Barber, 1994a
Genotoxicity – Chromosomal Aberration	Chromosomal aberration assay (Similar to OECD 473) with CHO cells	Negative	Barber, 1994a
Reproductive Toxicity	OECD 416: diet (0.3, 0.6, 1.0%), rat	1.0% for reproductive toxicity[1] F0: 447-614 mg/kg (male), and 595-1,349 mg/kg (female) F1: 552-893 mg/kg (male), and 697-1,549 mg/kg (female) 0.3% for parental and offspring toxicity[1] F0: 133-182 mg/kg (male), and 184-478 mg/kg (female) F1: 159-256 mg/kg (male), and 206-516 mg/kg (female)	Stump, 2001a
Developmental Toxicity	OECD 414: diet (0.3, 0.6, 1.0%), rat	0.6% (458 mg/kg) for maternal toxicity 1.0% (747 mg/kg) for fetal toxicity	Stump, 2001b
	Other: developmental effects in male rats assoc. with anti-androgenicity; Dams were treated for 10 days (GD 14 – PND 3), 750 mg/kg (gavage)	No adverse effects reported	Gray, 2000
	Other: Uterotrophic assay, 3 days (PND 19 - 21), 2,000 mg/kg (gavage)	No adverse effects reported	Stump, 2001c

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vitro Studies

The metabolic hydrolysis rate of DEHT, as determined by the formation of free 2-ethylhexanol (2-EH), was studied in vitro using a rat intestinal homogenate (Barber et al., 1994b). The half-life for disappearance of the di-ester parent molecule was 53.3 minutes. Importantly, the stoichiometry of the reaction at termination showed that 1.97 moles of 2-EH were formed per mole of DEHT, indicating complete hydrolysis to terephthalic acid (TPA). In contrast, the stoichiometry of the reaction with DEHP was one mole of 2-EH formed per mole of DEHP, indicating incomplete hydrolysis to mono(2-ethylhexyl) phthalate (MEHP).

In vivo Studies

The systemic absorption and metabolism of DEHT was studied in vivo by administering [^{14}C]-DEHT in corn oil by oral gavage (100 mg/kg) to 10 adult male SD rats (Barber et al., 1994b). Urine, feces and expired air were collected daily for 144 hours and analyzed for the presence of radioactivity and metabolites. At study termination, 93% of the total administered radioactivity was recovered. Most of the recovered radioactivity was found in the feces (56.5%) and urine (31.9%), while 3.6% was isolated in expired air (as $^{14}CO_2$) and 1.4% remained with the carcass. Urinary and fecal recovery rates peaked by 10 hours with > 95% of the total excreted amount recovered within 24 hours (> 99% by 48 hours). The mean amount of non-metabolized [^{14}C]-DEHT recovered in the feces was 36.6% of the total dose and the percentage of the total DEHT dose recovered in the urine (as unlabelled TPA) was 50.5%. In total, 90.7% of the dose was accounted for as either unchanged DEHT in feces, unlabelled TPA in urine, or as $^{14}CO_2$ in expired air. This balance sheet thus limits the amount of mono(2-ethylhexyl)terephthalate (MEHT) and its metabolites to a maximum of only 9.3% of the orally administered dose.

Studies in Humans

In vitro Studies

The rate of percutaneous absorption of DEHT through dermatomed sections of human skin was measured in an in vitro study (Guerin and Taylor, 2002). In this study, an excess of DEHT was applied to sections of human skin contained in glass diffusion cells. The measured absorption rate (mean ± SD) was 0.103 ± 0.052 μg/cm^2/hr. Using the definitions suggested by Marzulli, et al. (1969), the test substance would be classified as "extremely slow" with respect to its absorption through human skin. These data allow the estimation of uptake in man following dermal exposure to the test substance, assuming that skin absorption in man is similar to that observed in this in vitro study. For example, if excess test substance was to be in contact with an area of skin equivalent to both hands (approximately 720 cm^2, 70-kg human) continuously for 1 hr, then the calculated internal dose would be 1.06 μg/kg.

Conclusion

The results from the in vitro experiment indicate that DEHT is capable of undergoing complete hydrolysis in the intestine to form terephthalic acid (TPA) and 2-ethylhexanol (2-EH). After oral administration to rats, most of 14C-labeled DEHT was eliminated in the feces (56.5%) and urine (31.9 %), with smaller amounts in expired air (3.6%). The vast majority of the material in the feces was unchanged DEHT (36.6 % of the total dose) and 50.5 % of the dose was detected as

terephthalic acid in the urine. Since an additional 3.6 % of the dose was excreted as CO_2, the maximum amount of the monoester, mono-ethylhexyl terephthalate (MEHT) that could have been formed was 9.3 % of the dose. DEHT is also not readily absorbed through the skin.

3.1.2 Acute Toxicity

Studies in Animals

Dermal

The dermal LD_{50} value in guinea pigs was > 19,670 mg/kg (Gordon, 1975).

Oral

The oral LD_{50} values for rats and mice were > 5,000 mg/kg and > 3,200 mg/kg, respectively (Shepard, 1994; Gordon, 1975).

Conclusion

Acute toxicity testing of DEHT in laboratory animals indicates that this substance has a low potential for acute toxicity.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Guinea pigs exhibited slight irritation characterized by moderate to severe edema following a 24-hour exposure up to 20 ml/kg of DEHT under an occlusive wrap (Gordon, 1975). The study was a component of a dermal toxicity study performed under 24 hour occlusion and only one animal per concentration was tested. Therefore, its reliability as a skin irritation study is limited.

Studies in Humans

Human volunteers exposed to a 0.5% concentration of DEHT in acetone showed very little evidence of irritation (Lockhart, 2001a).

Eye Irritation

Studies in Animals

Results from eye irritation studies in rabbits indicate that DEHT is only slightly irritating, with the clinical signs consisting only of an erythema of the conjunctival tissues (Gordon, 1975). All eyes were completely normal by 48 hours post exposure.

Conclusion

Results of dermal irritation studies in guinea pigs and humans and eye irritation studies in rabbits show that DEHT may cause slight skin and eye irritation.

3.1.4 Sensitisation

Studies in Animals

Skin

Guinea pigs were exposed by an injection into the footpad to a 1% solution of DEHT. One-week later they were challenged with a dermal application of 1% DEHT. No significant signs of sensitization were observed 24- and 48-hours after challenge (Sharp, 1975).

Studies in Humans

Skin

In human volunteers, 203 participants completed a Modified Draize Procedure that involved nine dermal applications of 0.5% DEHT in acetone using a semi-occluded patch over a three-week induction period (Lockhart, 2001b). Induction was followed by an approximate two-week rest period followed by a challenge of a single application of test material to naïve skin at a naïve site. Under the conditions of this study, DEHT was found to be nonirritating and did not induce any evidence of sensitization

Conclusion

Results from studies in both guinea pigs and humans indicated no evidence of an induction of contact sensitization by DEHT

3.1.5 Repeated Dose Toxicity

Studies in Animals

Inhalation

Male SD rats exposed by inhalation to a single aerosol concentration of 46.3 mg/m^3 DEHT for 10 days (6 hr/day) demonstrated no overt toxicity (Gordon, 1986). No adverse findings were observed in the following parameters: mortality, clinical signs, body weight, hematology, serum chemistries, organ weights, and gross and microscopic pathology. The NOEL for this study was 46.3 mg/m^3.

Oral

Male SD rats (5/dose) given 0, 0.1, or 1.0 % DEHT in feed for 10 days (equivalent to 0, 85, or 885 mg/kg/day, respectively) showed no signs of overt systemic toxicity (Gordon, 1986). There were no mortalities, and body weight gains were comparable to control for all groups. All hematology determinations and clinical chemistries were comparable to the controls. No differences were noted in the weights of major organs, and there were no gross or histopathologic changes noted at any dose. The no observable effect level (NOEL) for this study was considered to be 1%.

Because o-phthalate esters are known to induce peroxisome proliferation in the liver of rats, DEHT was tested for its ability to induce peroxisome proliferation. F344 rats (5/sex/dose) were fed diets containing 0, 0.1, 0.5, 1.0, 1.2, or 2.5 % (approximately 0, 100, 500, 1000, 1250, and 2000 mg/kg/day) DEHT by weight for 21 days (Topping, et al., 1987). The no observable effect level (NOEL) for this study was 0.5%. Feed consumption in the 2.5% DEHT group was substantially reduced, which resulted in significantly decreased body weight gains. Animals consuming 1.2% or less DEHT demonstrated body weight gain similar to the control animals. Relative liver weights were increased at 2.5% in both sexes and at 1.0% and 1.2% in females due to slightly lowed terminal body weights. Induction of peroxisomes in the liver did not occur at 1.2% DEHT. Animals fed a diet containing 2.5% DEHT showed slight hepatic peroxisome proliferation.

However, since there was such a large reduction in food consumption and body weight gain at this dose, it cannot be concluded that 2.5% DEHT alone caused this change. Feed intake restriction alone has been shown to double the peroxisomal oxidizing activity of liver in rats (Ishii, et al., 1980).

In a 13-week study of DEHT, SD rats (20/sex/dose) were given 0, 0.1, 0.5, or 1.0 % DEHT in the diet for 90 days (approximately 0, 54, 277, and 561 mg/kg/day for males and 0, 61, 309, and 617 mg/kg/day for females) (Barber and Topping, 1995). The NOEL reported in this study was 0.5% in the diet (approximately 277 and 309 mg/kg/day in males and females, respectively). Increased relative liver weight was noted in males and females treated with 1.0 %. The effect on relative liver weight was not significant when expressed as a function of brain weight. Occasional changes noted in some blood parameters of rats treated with 0.5 and 1.0 % DEHT were not considered to be biologically significant. While these effects were statistically significant, the magnitude of the changes was small (< 5%) and not dose-dependent. No treatment-related changes were seen in the serum clinical chemistries. Microscopic examination did not reveal any treatment-related abnormalities in any tissue, including the testes, at any dose level. Additionally, there was no evidence of peroxisome proliferation (based upon morphometric analyses) in animals fed 1% DEHT for 90 days.

Thus, the terephthalate (para-phthalate) acid ester, DEHT, is not a peroxisome proliferator triggering the biochemical and cellular changes in the liver that are common for the phthalate (ortho-phthalate) acid ester DEHP.

Conclusion

Several studies have been conducted that have evaluated the toxicity of DEHT in rats following repeated exposures. In total, they demonstrate that DEHT has a low potential to induce toxicity following repeated exposures. The no observable effect level (NOEL) in the oral study of the longest duration (90 days, dietary exposure) was 0.5% (277 - 309 mg/kg in males and females, respectively), and the only effect observed in rats treated for 90 days with 1.0 % was increased relative liver weight

3.1.6 Mutagenicity

In vitro Studies

Mutation tests included an Ames test using a method similar to OECD 471 with Salmonella strains TA1535, TA1537, TA1538, TA98, and TA100, with test concentrations up to 10,000 µg/plate (the protocol limit of the test). An additional mutation assay followed guidelines similar to OECD 476 (HGPRT assay), with Chinese hamster ovary (CHO) cells exposed to DEHT concentrations up to the cytotoxic limit (20 nl/ml). Results of both tests were negative. The chromosomal aberration assay followed guidelines similar to OECD 473. In this experiment, structural damage was not induced in CHO cells exposed to DEHT at concentrations up to 1,000 nl/ml (the protocol limit of the test).

Conclusion

DEHT has been tested for genetic toxicity in assays assessing both mutagenicity (Ames and HGPRT) and aberrations with and without metabolic activation (Barber, 1994a). All studies were negative, indicating that DEHT is not genotoxic.

3.1.7 Carcinogenicity

There are no carcinogenicity data for DEHT. However, concern over this endpoint is not believed to be significant as DEHT is not considered to be genotoxic and does not induce liver peroxisome proliferation. Furthermore, DEHT is metabolized to 2-EH and TPA, both of which have been tested for carcinogenicity (CIIT, 1983 and Astill et al., 1996). Based on the results of these studies, neither was deemed to be a carcinogenic concern. The OECD has reviewed both these compounds (2-EH: SIAM 3 and TPA: SIAM 12) without significant concern over this endpoint.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

The reproductive toxicity of DEHT has been assessed through a two-generation study in rats following OECD test guideline 416. Groups of male and female SD rats were given 0, 0.3 0.6, or 1.0% DEHT in the diet (see Table 2 and dossier for mg/kg/d doses) (Stump, 2001a). The F0 animals received the diets for at least 70 days prior to mating and until termination of the generation; the F1 generation received diets following weaning (beginning on PND 22). All females were allowed to deliver and rear their pups to weaning (lactation day 21). Mean maternal body weights and body weight gains were reduced for F0 and F1 females in the 1.0% group throughout pregnancy. Mean maternal body weights were also reduced for the F0 and F1 females in this group throughout lactation. Decreased mean terminal body weights were noted in F1 males and females given 0.6 or 1.0% test material. Three F0 and seven F1 females in the 1.0% group were found dead or near death following weaning of their pups. Deaths were not correlated to any histopathologic change in tissues. No test-article related deaths were observed in the F0 or F1 females at the mid- and low-dose levels or in F0 or F1 males at any dose level. Reproductive parameters (fertility, mating, days between pairing and coitus, gestation, parturition, and estrous cycling) were unaffected by test article at any dose level during the F0 and F1 generations. Mean litter sizes, numbers of pups born, percentages of males per litter at birth and postnatal survival were unaffected by parental treatment at all concentrations. The NOAEL for reproductive toxicity was considered by the investigators to be 1.0% in the diet, and the NOAEL for parental and offspring toxicity was 0.3%.

Developmental Toxicity

The developmental toxicity of DEHT has been evaluated in a study following OECD test guideline 414 (Stump, 2001b). Groups of pregnant SD rats were treated with 0, 0.3, 0.6, or 1.0% DEHT in the diet (226, 458 and 747 mg/kg/d) from Day 0 of gestation until Day 20. On Day 20, all animals were euthanized, and the uterus and contents excised by caesarean section. The uterus and contents were weighed, and the fetuses removed from the amniotic sacs. The position and number of fetuses were recorded. The number of viable and non-viable fetuses, resorptions, and implantation sites were also recorded. Each fetus was weighed and examined for external abnormalities and visceral abnormalities. The head of one-half the total number of fetuses per litter was removed and preserved in Bouin's fluid for subsequent sectioning. The remaining carcasses of all animals were eviscerated and preserved for staining with Alizarin Red S and Alcian Blue for skeletal evaluation. There was no evidence of developmental toxicity, and no effect of treatment on the number of viable fetuses. No visceral or skeletal anomalies were attributed to treatment. The NOEL for maternal toxicity was 0.6%, and the NOEL for developmental toxicity was 1.0%. Effects observed in dams treated with 1.0% were reduced body weight and increased liver weight.

Gray et al. (2000) evaluated the ability of DEHT to induce anti-androgenic like effects in male offspring. Pregnant SD rats were given 0 or 750 mg/kg/day DEHT by gavage from gestation day (GD) 14 until post-natal day (PND) 3. No changes in anogenital distance, testes weight, testes descent, testes lesions, presence of areolas/nipples or vaginal pouch, reproductive organ weights, reproductive organ malformations, or mating behavior of male offspring were observed in the treated animals.

The estrogenic potential of DEHT was assessed through a uterotrophic assay (Stump, 2001c). Groups of 10 immature female SD rats were given DEHT orally by gavage once daily on PND 19-21 at dose levels of 20, 200, or 2000 mg/kg/day. Animals were euthanized approximately 24 hours later and their uterus was removed and weighed. A reduction in mean body weight gain was observed at the highest dose level. However, no effects on uterine weight or calculated fluid content were observed at any dose. The positive control group given ethinyl-estradiol showed a 3-4 fold increase in uterine weight. It was concluded that DEHT does not possesses estrogenic activity.

Conclusion

The results of the two-generation study, in conjunction with the study described above (see Section 3.1.5) where there was an absence of any histological alterations in reproductive organs following 90-days of exposure indicate that DEHT does not induce reproductive toxicity at concentrations up to 1.0%. Several studies have been conducted that demonstrate the low likelihood that exposure to DEHT will induce developmental toxicity, and indicate that DEHT does not possesses anti-androgenic or estrogenic properties. The NOAEL established in the dietary reproduction study (0.3%) and the NOELs in the developmental study for parental and maternal toxicity (0.6%) are consistent with the repeated dose NOELs of 0.5%.

3.2 Initial Assessment for Human Health

DEHT poses a low hazard to human health based on the lack of toxicity in animal studies. Essentially minimal evidence of toxicity was seen at the highest dose assessed in any of the SIDS endpoint studies conducted. The oral LD_{50} values were > 3,200 mg/kg in mice and > 5,000 mg/kg in rats. DEHT induces only slight skin and eye irritation and is not a contact sensitizer in humans. All studies assessing for genotoxicity potential (chromosomal mutations and aberrations) were negative. No observable effects were noted in rats after 90 days of repeated exposure to DEHT in the diet at levels as high as 0.5% (277-309 mg/kg/d). No evidence of reproductive or developmental toxicity was observed in rats exposed to dietary concentrations of DEHT as high as 1%. Studies performed to understand the metabolic fate of DEHT demonstrate that the material is not readily absorbed following oral administration and is capable of undergoing complete metabolic hydrolysis to TPA and 2-EH. Both TPA and 2-EH have undergone review by the OECD (SIAM 3 and 12). Results of an in vitro dermal absorption study also indicate that DEHT does not readily pass through skin.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

The acute toxicity of DEHT was measured in fish, invertebrates, and algae. Both benthic and pelagic organisms, as well as freshwater and marine species, were tested. The available data are summarized in Tables 3-5.

Toxicity test data on two freshwater fish species are available, including fathead minnow (Pimephales promelas) and rainbow trout (Salmo gairdneri). For freshwater invertebrates, the pelagic daphnid, Daphnia magna and the Ramshorn snail, Planorbella trivolvis, were tested. The benthic marine invertebrate Eastern Oyster Crassostrea virginica also was tested. The green alga Selenastrum capricornutum (recently renamed Pseudokirchneriella subcapitata) also was tested. The NOECs were at the highest concentrations tested in all studies, which exceeded the limit of solubility. Therefore, the studies showed no effects at the level of solubility and are adequate to assess the acute and chronic aquatic toxicity of DEHT.

In the majority of the aquatic studies, test concentrations were analytically confirmed. The finding that the concentrations present in these studies exceeded the solubility of the material determined in the critical study (0.0004 mg/l) is not surprising, since organic solvents (DMF or acetone) were present in the dosing solutions that were added to the water. The presence of organic solvents in the test water would be expected to increase solubilization of the material. DEHT is also known to have a strong potential to adhere to trace amounts of particulate matter, which can serve as adsorptive sites for the test substance and effectively increase its apparent solubility.

Chronic Toxicity Test Results

The chronic toxicity of DEHT has been studied with two species (Rainbow trout and Daphnia magna)(Tables 3-4). The NOEC was at the highest concentration tested and exceeded the limit of solubility in both studies. As mentioned previously, test conditions in these studies were designed to promote solubilization.

A flow-through 60-day post-hatch early life stage toxicity study of DEHT to rainbow trout (Salmo gairdneri) was conducted to estimate the Maximum Acceptable Toxicant Concentration (MATC) limits. Hatchability of rainbow trout eggs after 11 days of continuous exposure to 0.014, 0.024, 0.047, 0.15, and 0.28 mg/l was not significantly affected when compared to control. Likewise, survival of fry between hatch and 60 days of exposure to all test concentrations was not reduced in a significant manner. Growth of trout fry, as measured by wet weight after 60 days of exposure to all test concentrations, was not significantly reduced. Based on these data, the MATC was determined to be >280 µg/l (measured)(ABC Laboratories, 1986a).

A 21-day full life cycle toxicity test using Daphnia magna under flow-through conditions was conducted using a high nominal concentration of 1.0 µg/l with a dilutor system providing four additional 50% dilution concentrations (0.50, 0.25, 0.13, and 0.063 µg/l)(Cafarella, 2002). A control and solvent control were also included in the test. The test solutions for each treatment level were measured on days 0, 7, 14, and 21. Mean measured test concentrations were 0.039, 0.084, 0.17, 0.35, and 0.76 ug active ingredient/liter. The biological effects monitored were survival/immobility, reproduction, organism length and dry weight. No biologically relevant statistical differences were detected between the controls and treated organisms (21-day EC_{50} >0.76 µg/l, 21-day NOEC = 0.76 µg/l).

Table 3 Acute and Chronic Toxicity of Di-(2-ethylhexyl) Terephthalate (DEHT) to Fish

Organism	Test Type	Results	Reference
Fathead minnow *Pimephales promelas*	96-h static, freshwater	$LC_{50} \geq 984{,}000$ µg/l[1,2] NOEC[3] $\geq 984{,}000$ µg/l[1,2]	Ewell, 1986
Rainbow trout *Salmo gairdneri*	7-d, flow-through, freshwater	$LC_{50} \geq 250$ µg/l[4] NOEC[3] ≥ 250 µg/l[4]	ABC Laboratories, Inc., 1985b
Rainbow trout *Salmo gairdneri*	71-d, flow-through, freshwater	NOEC[5] ≥ 280 µg/l[4]	ABC Laboratories, Inc., 1986a

1 An oily film was observed on the surface, indicating that the material was not soluble at this concentration
2 Nominal concentration

3 Survival endpoint

4 Acetone was added to aid solubilization

5 Endpoints of hatchability, survival, and growth

Table 4 Acute and Chronic Toxicity of Di-(2-ethylhexyl) Terephthalate (DEHT) to Aquatic Invertebrates

Organism	Test Type	Results	Reference
Water flea *Daphnia magna*	48-h, static, freshwater	EC50 ≥ 1.4 µg/l[1] NOEC[2] ≥ 1.4 µg/l[1]	Light, 2002
Planorbid snail *Planorbella trivolvis*	96-h static, freshwater	$EC_{50} \geq 984{,}000$ µg/l[3,4] NOEC[2] $\geq 984{,}000$ µg/l[3,4]	Ewell, 1986
Eastern Oyster *Crassostrea virginica*	96-h flow-through, marine	EC_{50}[6] ≥ 624 µg/l[5] NOEC[6] ≥ 624 µg/l[5]	Battelle New England Research Laboratory, 1986b
Water flea *Daphnia magna*	21-day, flow through, freshwater	EC50[7] ≥ 0.76 µg/l[5] NOEC[7] ≥ 0.76 µg/l[5]	Cafarella, 2002

1 DMF was added to aid solubilization

2 Survival endpoint

3 An oily film was observed on the surface, indicating that the material was not soluble at this concentration

4 Nominal concentration

5 Acetone was added to aid solubilization

6 Survival and shell deposition endpoints

7 Endpoints: Survival, reproduction, growth (length & dry weight)

Table 5 Acute Toxicity of Di-(2-ethylhexyl) Terephthalate (DEHT) to Algae

Organism	Test Type	Results	Reference
Green alga *Selenastrum capricornutum*	72-h static, growth inhibition, freshwater	$EC_{50} \geq 860$ µg/l[1] NOEC[2] ≥ 860 µg/l[1]	Beach, 2000

1 DMF was added to aid solubilization

2 Endpoints: biomass and growth rate

4.2 Terrestrial Effects

Acute Toxicity Test Results

Three plant species were evaluated in a seedling growth test for 14 days. The plants were exposed to ^{14}C-DEHT via the nutrient solution that was added to the plants grown in sand. The EC_{50} values for ryegrass (Lolium perenne) and radish (Raphanus sativus) were > 1400 µg/l, and for soybean (Glycine max) were > 1500 µg/l (ABC Laboratories, 1986b). No biologically deleterious effects were noted on the ryegrass and radish at 1400 µg/l, and soybean at 1500 µg/l - the highest concentration tested, and concentrations that exceeded aqueous solubility.

Chronic Sediment Toxicity Test Results

Because DEHT would have a strong tendency to sorb to sediments in the environment, a Sediment-Water Chironomid Toxicity Test using Spiked Sediment (OECD Method 218) was conducted on the material. Five concentrations of DEHT ranging from 92.1-950 mg/kg were tested. The test species utilized was *Chironomus riparius* and the endpoint was the number of live, emerged adult midges. The results indicated that the 28-day EC_{50} (reduction in emergence) was greater than 950 mg/kg. The 28-day EC_{50} (development rate) was also greater than 950 mg/kg. There were no significant differences between the numbers of males and females that emerged. A subset of replicates was sacrificed to determine the 10-day larval survival and growth data. There were no statistical differences in growth (weight) between the control and any of the test groups at 10 days. There were statistical differences in survival between the control and some of the test groups, but the number of larvae surviving on day 10 was similar to the number observed emerging to adult flies on day 28. The No Observable Effect Concentration for emergence was 180 mg/kg. (Sewell and McKenzie, 2004)

4.3 Other Environmental Effects

The potential for accumulation of DEHT in aquatic organisms was studied in a bioconcentration test using the Eastern Oyster (Crassostrea virginica)(Battelle, 1986a). The sample of ^{14}C-DEHT used in the study contained a ^{14}C tag in the 2-ethylhexyl side chain. The oysters were exposed to 50 µg/l ^{14}C-DEHT (nominal concentration, dissolved in acetone to increase solubility) in salt water continuously for 24 days, followed by 14 days of depuration in flowing DEHT-free salt water. Total radioactivity was measured periodically in the test water and in the soft tissue of the oysters. By Day 21 of the exposure phase, uptake of ^{14}C-DEHT appeared to be at steady state. The calculated BCF value at steady state was 393. The initial loss of ^{14}C-DEHT during the depuration phase was rapid. Within 7 days, radioactivity in the soft tissue of the oysters decreased from 15 µg/g to 4 µg/g (73%). Thereafter, the radioactivity in the tissues remained relatively constant, suggesting that the DEHT may have been metabolically converted into cellular tissue. The presence of the ^{14}C tag in the alkyl side chain would allow this metabolic result, leading to an artificially increased BCF value.

A 3-hour activated sludge respiration inhibition test was performed using activated sludge from a domestic wastewater treatment plant (Moulton, 2003). The sludge microorganisms were exposed to five concentrations of the test substance. The respiration rate, expressed as oxygen consumption by the microbes in mg O_2 per liter per hour, was measured under defined conditions following the 3-hour exposure period. Inhibition values were calculated by comparing test respiration rates to negative control rates. The 3-hour respiration inhibition test resulted in an EC_{50} value >10 mg/l and a NOEC of 10 mg/l, the highest concentration tested. Thus, DEHT is not expected to inhibit respiration of secondary wastewater treatment microorganisms.

4.4 Initial Assessment for the Environment

An OECD toxicity test using DEHT spiked sediments indicated that the EC50 was greater than the highest concentration recommended by the method.

DEHT is a high boiling liquid (boiling point 383°C at 1015 hPa) with a very low vapour pressure (estimated to be 2.85 E-5 hPa at 25°C by EPIWIN). It has a melting point of -48°C, a water solubility of 0.0004 mg/l and an EPIWIN-estimated octanol/water partition coefficient of 8.39. The atmospheric photodegradation half-life is 0.487 days (5.84 daylight hours). Based on its molecular structure, DEHT is not anticipated to undergo rapid hydrolysis in the presence of water. Level III fugacity modeling assuming equal distribution indicates 0.743% to air, and 7.26% to water with greater percentages in the soil and sediment compartments (28% and 64%, respectively). These results are supported by a Koc value of 1.62 E+5. While the vapour pressure of DEHT is very low, the Henry's Law Constant is relatively high (1.02 E-5 atm-m^3/mol) due to the substance's offsetting low aqueous solubility. A biodegradation study failed to show that the material was "readily biodegradable" under the method and conditions of the test, but did show 40.2% conversion to CO2 in 28 days indicating that the material is ultimately biodegradable. Results of an activated sludge respiration inhibition test indicate that DEHT is not toxic to wastewater microbes. Studies assessing acute and chronic toxicity to fish (Fathead minnow and Rainbow trout) and invertebrates (*Daphnia magna*, Planorbid snail, Eastern oyster), and acute affects on algal (*Selenastrum capricornutum*) growth showed no effects at water concentrations that were often significantly greater than its limit of solubility in distilled, deionized water that is free of particulate matter (0.0004 mg/L). Terrestrial plant growth in three species was not affected by DEHT exposure. An OECD sediment-water chironomid toxicity test using spiked sediments indicated that the EC50 was greater than the highest concentration recommended by the method (1000 mg/kg nominal, 950 mg/kg measured) and the NOEC was 180 mg/kg. A bioconcentration study in oysters indicated that the material has a medium to low potential to bioconcentrate (BCF = 393). However, due to its propensity to be eliminated by higher trophic organisms, it is not expected to bioaccumulate.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work because of its low hazard profile.

Adequate information exists for DEHT for screening purposes and to indicate that DEHT poses low hazard to the environment and to mammalian species.

6 REFERENCES

Analytical Bio-Chemistry Laboratories, Inc. (1985a). Shake flask biodegradation of di(2-ethylhexyl) terephthalate (DOTP). Unpublished Fate Test Report #32170.

Analytical Bio-Chemistry Laboratories, Inc. (1985b). Dynamic 7-day acute toxicity of di(2-ethylhexyl)terephthalate (DOTP) to rainbow trout (*Salmo gairdneri*). Unpublished Toxicity Test Report #32167.

Analytical Bio-Chemistry Laboratories, Inc. (1986a). Early life stage toxicity of di(2-ethylhexyl)terephthalate (DOTP) to rainbow trout (*Salmo gairdneri*) in a flow-through system. Unpublished Toxicity Test Report #32168.

Analytical Bio-Chemistry Laboratories, Inc. (1986b). Effects of di(2-ethylhexyl) terephthalate (DOTP) on the early seedling growth of ryegrass, radish, and soybean. Unpublished Toxicity Test Report #33290.

Astill BD, Gingell R, Guest D, Hellwig J, Hodgson JR, Kuettler K, Mellert W, Murphy SR, Sielken RL Jr. and Tyler TR (1996). Oncogenicity testing of 2-ethylhexanol in Fischer 344 rats and B6C3F1 mice. Fund App Toxicol. **31**(1), 29-41.

Barber ED (1994a). Genetic toxicology testing of di(2-ethylhexyl) terephthalate. Environ Molec Mutagen. **23**, 228-233.

Barber ED, Fox JA and Giordano CJ (1994b). Hydrolysis, absorption and metabolism of di(2-ethylhexyl) terephthalate in the rat. Xenobiotica **24**, 441-450.

Barber ED and Topping DC (1995). Subchronic 90-day oral toxicology of di(2-ethylhexyl) terephthalate in the rat. Food ChemToxicol. **33**, 971-978.

Battelle - New England Marine Research Laboratory (1986a). The bioconcentration and elimination of ^{14}C-bis(2-ethylhexyl) terephthalate by eastern oysters (Crassostrea virginica). Unpublished Fate Test Report – Study No. N-0950-2203.

Battelle - New England Marine Research Laboratory (1986b). The oyster shell deposition test to assess the acute effects of bis(2-ethylhexyl) terephthalate on eastern oysters (Crassostrea virginica). Unpublished Toxicity Test Report - Study No. N-0950-2203.

Beach SF (2000). Bis(2-ethylhexyl)terephthalate - A growth inhibition limit test with the alga, *Selenastrum capricornutum*. Eastman Kodak Company Rochester, NY; Unpublished Report #ES-2000-030.

Beeler AD (1976). Plast. Eng. **32**(7), 40-41.

Cafarella MA (2002). Eastman Plasticizer 168 – Full life cycle toxicity with water fleas, Daphnia magna under flow-through conditions. Springborn Smithers Laboratories, Wareham MA, (Unpublished report) Study No.: 1852.6193.

CIIT (1983). Chronic dietary administration of terephthalic acid. CIIT Docket 20124.

Eastman Chemical Company. 2001. Material Safety Data Sheet.

Ewell WS (1986). Acute aquatic effects of di (2-ethylhexyl) terephthalate on three freshwater species. Unpublished Eastman Kodak Company Report #ES-86-042.

Gordon D (1975). Acute toxicity of di (2-ethylhexyl) terephthalate. Eastman Kodak Company, HAEL No. 74-0170 Acc. No. 907040 (Unpublished data).

Gordon DR (1986). Two-week oral and inhalation studies of di (2-ethylhexyl) terephthalate in the rat Eastman Kodak Company, HAEL No. 74-0170 Acc. No. 907040 (Unpublished data).

Gray LE Jr., Ostby J, Furr J, Price M, Veeramachaneni DN and Parks L (2000). Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol. Sci. **58,** 350-365.

Guerin TS and Taylor L (2002). Eastman Plasticizer 168 -Measurement of the in vitro rate of percutaneous absorption through human skin, HAEL No.: 2000-0213; Eastman Kodak Company, Rochester, NY (Unpublished data).

Guinn RJ (2003). Summary of di-(2-ethylhexyl) terephthalate short-term chronic toxicity tests using the test species *Ceriodaphnia dubia.* Aquatic Toxicology Section of the Environmental Services Laboratories, Tennessee Eastman Division, Kingsport, Tennessee (Unpublished data).

Ishii H, Horie S and Suga T (1980). Physiological role of peroxisomal β-oxidation in liver of fasted rats. J. Biochem. (Tokyo) **87**, 1855-1858.

Klimisch H-J, Andreae M and Tillmann U (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul. Toxicol. Pharmacol. **25**, 1-5.

Light GC (2002). Eastman Plasticizer 168 – An acute aquatic effects limit test with the Daphnid, *Daphnia magna*. Unpublished Eastman Kodak Company Report #ES-2002-011.

Lockhart LK (2001a). Evaluation of primary irritation potential in humans (three 24-hour applications). Hill Top Research Inc., (Unpublished data) HTR Study Number: 01-108653-70.

Lockhart LK (2001b). Repeat insult patch test (modified Draize procedure). Hill Top Research Inc., (Unpublished report) HTR Study Number: 01-108654-70.

Marzulli FN, Brown, DWC and Maibach HI (1969). Techniques for studying skin penetration. Toxicol. Appl. Pharmacol**. Suppl.3**, 76-83.

Moulton ME (2003). Activated sludge respiration inhibition test (OECD 209 and EEC/Annex V Supplement) Eastman Kodak Company Rochester, NY; Unpublished data, Study No. EN-620-907040 –A.

Sewell IG and Mckenzie J (2004). Eastman DEHT: Sediment-Water Chironomid Toxicity Test Using Spiked Sediment. OECD Guideline No. 218. Safepharm Laboratories Limited, (Unpublished report) SPL Project Number 1328/065

Sharp RL (1975). Toxicology and health hazard summary of chemical: Bis (2-ethylhexyl) terephthalate (Revised). Eastman Kodak Company, (Unpublished report) Lab 74-170 and 75-35, Acc. No. 907040.

Shepard KP (1994). Di (2-ethylhexyl) terephthalate; Alternate name: Eastman DOTP Plasticizer, PM 4595, Acute oral toxicity study in the rat. Eastman Kodak Company, (Unpublished report) HAEL No. 93-0128, KAN: 907040; TX-94-33.

Stump DG (2001a). A dietary two-generation reproductive toxicity study of di-2-ethylhexyl terephthalate in rats. WIL Research Laboratories, (Unpublished report) Laboratory Study Number WIL-387001.

Stump DG (2001b). A dietary prenatal developmental toxicity study of di-2-ethylhexyl terephthalate in rats. WIL Research Laboratories, (Unpublished report) Laboratory Study Number WIL-387002.

Stump DG (2001c). A uterotrophic assay of di-2-ethylhexyl terephthalate administered orally to immature female rats. WIL Research Laboratories, (Unpublished report) Laboratory Study Number WIL-387003.

Topping DC, Ford GP, Evans JG, Lake BG, O'Donoghue JL and Lockhart HB (1987). Peroxisome induction studies on di(2-ethylhexyl)terephthalate. Toxicol. Ind. Health **3**(1), 63-78.

US EPA. 1988. Inventory Update Report.