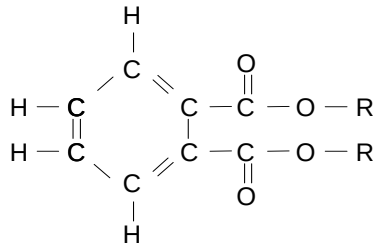
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	71888-89-6
Chemical Name	1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich (diisoheptyl phthalate ester)
Structural Formula	$C_{22}H_{34}O_4$ (based on di-C7 alkyl groups) Diisoheptyl phthalate ester has the following basic structure with R = C_6H_{13} to C_8H_{17} (primarily C_7H_{15}), where R is an alkyl group that can have various methyl branching patterns (the linear portion of the alkyl group can be referred to as the backbone of this moiety):  DIHP consists of at least 80% of methyl hexyl phthalate. Therefore the backbone (i.e. the longest linear C- chain) is predominantly C6. The methyl group branching can be found on different C positions of the hexyl backbone chain.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

DIHP has a low order of acute toxicity (oral LD_{50} greater than 10 mg/kg bw; dermal LD_{50} greater than 3.16 g/kg bw), is mildly irritating to the skin and eyes, is neither a skin nor a respiratory sensitiser, and is not mutagenic.

No repeated dose toxicity studies are available for DIHP. However a two-generation reproductive toxicity study has been conducted in rats (1000, 4500, or 8000 ppm in the diet for 70 days, prior to mating and through mating, gestation, and lactation periods) which can be used to evaluate this endpoint. No treatment related changes were observed in body weights, clinical observations or food consumption. The target organs were the testis, liver and the kidneys. There were no organ weight or pathological changes in rats of either sex at the 1000 ppm level. Therefore, this level has been selected as the NOAEL for the systemic toxicity and equates to an overall average dose to the males of 64 mg/kg bw/day. The average doses to the females were approximately 84 mg/kg bw/day during the premating period, 64 mg/kg bw/day during the mating period, and 162 mg/kg bw/day during lactation.

Reproductive effects in this two-generation study included decreased reproductive performance and fertility for both sexes in the F_1 generation at the highest dose level. Decreased mean sperm production rates and decreased testicular sperm concentration were observed in F_1 males, but this finding may have been an experimental artifact rather than a treatment related effect except in the high dose group. Several other effects such as: reduced anogenital distance, delays in balanopreputial separation, testicular abnormalities, changes in external genitalia, and retention of thoracic nipples were also noted at the highest dose level. Similar effects were also seen in the F_2 generation. Additional

effects included reductions in body weights along with decreased gonadal and spleen weights, and increased kidney, liver, and pituitary weights. There were also dose-related increases in the liver weights and correlating hepatocellular histopathology changes that are indicative of peroxisomal proliferation. The NOAEL for parental systemic toxicity in the F_0 and F_1 generations was 1000 ppm in the diet (in the range of 50 to 162 mg/kg bw/day) based on peroxisomal proliferation in the liver. The overall NOAEL for reproductive effects in males and females was 1000 ppm in the F_2 generation (in the range of 64 to 162 mg/kg bw/day for gestation - lactation periods).

A developmental study conducted on DIHP in rats using oral gavage at doses of 0, 100, 300, and 750 mg/kg bw/day on gestation days 6-20 showed a statistically significant decrease in mean body weight of the 750-mg/kg bw/day dams and increase in liver weights. Changes included an increase in the mean number of resorptions per litter and resorptions per implantation site with a concomitant decrease in live fetuses and live fetuses per implantation site. Fetal weight was significantly reduced and there was an increase in the incidence of fetuses with external, visceral and skeletal malformations compared to controls (9.8 vs. 1.0%). The developmental NOAEL was established at 300 mg/kg bw/day and the maternal NOAEL at 750 mg/kg bw/day. In assays to assess estrogenic activity (screening tests for competitive binding and gene expression using the estrogen receptor *in vitro*, and vaginal cornification and uterotrophic assays assessing estrogenic activities *in vivo*), DIHP showed no positive results.

DIHP was not tested for carcinogenicity.

Environment

Additional data from other similar phthalate ester (PE) substances (analogues) are used in this submission to support diisoheptyl phthalate ester (DIHP) and/or provide additional weight of evidence for select endpoints. The use of read-across data for single substances and within categories or "families" of substances has been used previously within HPV programs. Data from analogue PEs are used to augment the current database for DIHP on the basis that these substances exhibit common physicochemical, ecotoxicological and environmental fate properties.

Furthermore it has been shown that for environmental hazard assessment, it is possible to consider the use of analogue data from among PEs having a backbone alkyl chain length longer than 5 carbons. Indeed, the water solubility of these PEs is so low and no toxicity in fish, invertebrates, and algae is exhibited at their limit of solubility. And also, in general, their data can be applied across the range of increasing/decreasing alkyl side-chain carbon (C) numbers. The validity of applying read-across data for select aquatic toxicity endpoints as is done in this submission, is supported from a review of all directly comparable data for DIHP and the analogues.

To define select biological endpoints, measured analogue data are used from 5 PEs, namely 1,2-Benzenedicarboxylic acid, diheptyl ester or di-nC7 PE linear (CAS RN 3648-21-3), 1,2-Benzenedicarboxylic acid, heptyl undecyl ester, branched and linear or di-C7-11 PE (CAS RN 111381-90-9), 1,2-Benzenedicarboxylic acid, diisooctyl ester or di-C8 PE (CAS RN 27554-26-3), 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester or DEHP (CAS RN 117-81-7), 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich or DINP (CAS RN 68515-48-0).

Diisoheptyl phthalate (DIHP) is a liquid at 25°C with a reported vapor pressure of 9.3×10^{-7} hPa (25°C), water solubility of 0.017 mg/l (22°C), log Kow of 6.9 (25°C), melting point of -45°C, boiling point of 393°C (1,013 hPa), and density of 0.99 g/cm^3 (20°C).

Results of distribution modelling suggest that DIHP will partition primarily to the soil compartment (approximately 98%), with a small amount partitioning to sediment (approximately 2%). Volatilisation to air will not contribute to the loss of DIHP from terrestrial or aqueous habitats because it has a very low vapour pressure. Results of modelling confirm that only a negligible amount of DIHP is calculated to partition to air (<1.0%). However, the small fraction that may partition to air has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals. The DIHP half-life from hydroxyl radical attack is calculated as 7.2 hours (0.6 days based on a 12-hour day as this reaction occurs primarily during daylight hours). Aqueous photolysis and hydrolysis will not contribute to the transformation of DIHP in aquatic environments because it is either poorly or not susceptible to these reactions.

DIHP was shown to be readily biodegradable, based on a 28-day biodegradation study with a test substance concentration of 50 mg/L that resulted in approximately 80% biodegradation. DIHP is expected to sorb to organic matter in soil, sediment, and wastewater solids based on a log K_{oc} of 4.5.

The acute and chronic aquatic toxicity of DIHP has been evaluated using various species covering the three trophic levels. For select endpoints for which DIHP data were not available, which includes the alga endpoint, analogue data from similar substances were used including di-C8 PE and DINP. All studies were conducted by either developing water accommodated fraction (WAF) exposure solutions that were prepared at loading levels (100 or 10 mg/L) above the water solubility of DIHP or testing at concentrations (1 mg/L) using dispersants. On the basis of testing results with DIHP and/or analogues, it can be concluded that DIHP does not produce acute or chronic toxicity at or below its maximum attainable water solubility, which has been measured as 0.017 mg/L.

DIHP showed no effects on seed germination and growth at a concentration of 1000 mg/kg soil. Additionally, DIHP is not expected to be inhibitory to soil microorganisms, based on a respiration study using an analogue phthalate ester (DINP), at test substance/soil loadings as high as 10000 mg/kg soil. DIHP is not expected to exhibit effects to wastewater microorganisms, based on a study using an analogue phthalate ester (DEHP) at a test substance loading of 2000 mg/L that showed no inhibition to respiration in an activated sludge sample.

In the sediment, results obtained with an analogue phthalate ester that contains C7 alkyl groups (di-C7-11PE), showed no effect on survival and growth to two freshwater sediment species at a test substance loading of 3000 mg/kg sediment, suggesting that DIHP is not toxic to benthic organisms.

The potential for DIHP to bioaccumulate in fish is estimated to be low to moderate (BCF from 0.9 to 840), based on OECD Guideline and non-standard testing, on two analogues, di-nC7 PE and DEHP.

Exposure

DIHP production volume is between 20 000 and 200 000 tonnes per annum worldwide, with production sites in both Europe and in the USA.

DIHP is mainly used as an additive (plasticiser) to impart flexibility to polyvinylchloride (PVC) resins, which are largely used in the manufacture of flooring products. Furthermore, DIHP is not used in applications such as medical devices or toys for ethical and technical reasons.

DIHP released from its manufacture, which can occur when cleaning manufacturing systems, enters wastewater treatment facilities where it can be biodegraded or sorbed to sewage sludge.

The majority of PEs found in the environment likely comes from the slow release of these chemicals from polymer products as a result of weathering processes. Indeed, once PEs are produced and used in various products, emissions may occur during the end-use of these products. However, since most PEs are contained within a polymer matrix, emissions are retarded during the life of the polymer product.

Exposure to DIHP in the occupational setting has not been extensively measured but is expected to be low. Area monitoring and personal sampling data have been collected for airborne exposure to two other phthalate esters, e.g. butylbenzyl phthalate (BBP) and DINP, at two flooring manufacturers. The data show that at typical customer sites, measured airborne levels ranged from 0.01 to 1 mg/m^3. As a very conservative basis, assuming exposure at 1 mg/m^3 for 8 hours and 10 m^3 inhaled during a working day, and complete absorption of inhaled materials, this equates to an internal dose of 10 mg. Assuming that the typical worker weights 70 kg, this equates to a dose expressed on a body weight basis of 0.14 mg/kg/day.

There have not been any quantitative estimates of DIHP exposure in the general population, but it is expected to be low. There are recent estimates of exposures to a number of other phthalates within the US population based on a biomonitoring method developed by the United States Centers for Disease Control (U.S. CDC). Human exposures calculated from these estimates indicated that for DEHP, the phthalate ester most widely used in commerce, the

median exposures were less than 1 µg/kg/day. As production levels of DIHP are below those of DEHP, it would be reasonable to assume that exposures to DIHP would not exceed those of DEHP.

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

Human Health: The chemical possesses properties indicating a hazard for human health (reproductive toxicity). Given its use pattern, the chemical is a candidate for further work. Member countries are invited to perform an exposure assessment for workers and consumers and if necessary a risk assessment.

Environment: This chemical is currently of low priority for further work due to its low hazard potential in the environment.