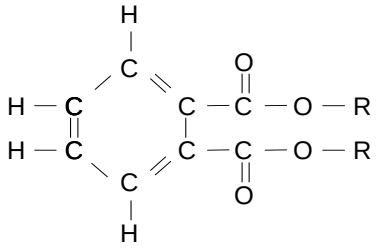
SIDS INITIAL ASSESSMENT PROFILE

Chemical Category	High Molecular Weight Phthalate Esters (HMWPE)
CAS Nos.	53306-54-0 68515-41-3 85507-79-5 68515-43-5 3648-20-2 68515-47-9 119-06-2
Chemical Names	1,2-benzenedicarboxylic acid, di-2-propylheptyl ester 1,2-benzenedicarboxylic acid, di-C7-9-branched and linear alkyl esters 1,2-benzenedicarboxylic acid, di-C11-branched and linear alkyl esters 1,2-benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters 1,2-benzenedicarboxylic acid, di-C11-alkyl ester 1,2-benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13 rich 1,2-benzenedicarboxylic acid, di-C13-alkyl ester
Structural Formula	Substances in the High Molecular Weight Phthalate Esters Category have the following basic structure with alkyl groups (R) as indicated for the CAS registry numbers (RNs) below:  53306-54-0 R=$C_{10}H_{21}$ (propyl branched) [100% branched] 68515-41-3 R=C_7H_{15} to C_9H_{19} (branched and linear) [>80% linear] 85507-79-5 R=$C_{11}H_{23}$ (branched, essentially methyl, and linear) 68515-43-5 R=C_9H_{19} to $C_{11}H_{23}$ (branched and linear) [>80% linear] 3648-20-2 R=$C_{11}H_{23}$ (branched) 68515-47-9 R=$C_{13}H_{27}$ (branched, essentially methyl) 119-06-2 R=$C_{13}H_{27}$ (branched)

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The High Molecular Weight Phthalate Ester (HMWPE) Category consists of esters with an alkyl carbon backbone with 7 carbon (C) atoms or greater. The category is formed on the principle that substances of similar structure have

similar environmental and toxicological properties. Data are available on substances that meet the category definition and which are, or are not members of the category, to demonstrate that the members of this category have similar biological activities and that, when used, read-across is an appropriate approach to characterize endpoints for select members of this category.

The HMWPE Category contains chemically similar substances, 1,2-benzenedicarboxylic acid reacted with branched and/or linear alkyl alcohols, which are referred to as the alkyl chains in the phthalate ester molecule. A phthalate ester (PE) molecule is produced by esterifying one molecule of benzenedicarboxylic acid (phthalic anhydride) with two alcohol molecules. The seven members of this category contain linear and/or branched diheptyl, dioctyl, dinonyl, didecyl, diundecyl, didodecyl, and/or ditridecyl PEs. The branched alkyl chains are composed of varying mixed isomers. The length of the alkyl chains varies by substance, but the total carbon number of the longest linear C-chain (or backbone chain) is predominantly C7 or greater. For the seven substances in the category described in this submission, the backbones range from C7 to C12. The backbones in all but one category member contain methyl branching, only the bis-propyl heptyl phthalate backbone contains propyl branching.

Due to similar chemical structure, category members are generally similar with respect to select physico-chemical properties or display an expected trend (see Table 1 in SIAR). From the available data, HMWPE members are also similar with respect to their biological activity in that they demonstrate few biological effects.

For PEs, the critical toxicological effects are development and reproduction. These aspects are very structure dependent, and are associated with molecules with a 4 to 6 carbon backbone. By contrast, PEs with 7 or more backbone carbons produce no detectable effects in reproduction and no adverse effects on development. From a very large toxicology database for phthalate esters, a structure activity can be demonstrated that best relates to the linear portion of the phthalate ester, rather than total carbon number. For example, DINP (di-isononyl phthalate ester, CAS No 68515-48-0 and 28553-12-0) and DIDP (di-isodecyl phthalate ester, CAS No 68515-49-1 and 26761-40-0), are not formally part of this category as they have been assessed previously, but satisfy the category definition (as in Table 2 of the SIAR). Furthermore, for environmental effects, PEs do not show any effects from C5 upwards (see reference in SIAR). Hence, the HMWPE Category is valid for both toxicological and environmental endpoints.

As mentioned, DINP and DIDP, meet the category definition in that their backbone lengths are predominantly C7 or above, and produce little, if any, effects of developmental or reproductive toxicity. The DINP and DIDP dossiers have not been included in detail in this category, as they have already been assessed in the OECD HPV program. However select data for these two substances will be used as supportive data to the category.

To correctly characterize selected endpoints for PEs, read-across techniques can be applied. Read-across is typically performed using measured or calculated data for an endpoint of interest for one or more like-substances to predict that endpoint for a similar substance without data.

Two general rules for read-across as they apply to PEs include:

- Chemical relatedness - the substance without data as well as the substance(s) with data are similar such that their physicochemical, biological, and toxicological properties would be expected to behave in a predictably similar manner or logically progress across a defined range. It is shown that for the environment assessment, read-across can be performed with HMWPE having a backbone chain length longer than 5 carbons. Indeed, since their water solubility is so low, there is no toxicity in fish, invertebrates, and algae for the HMWPE members at their limit of solubility. Read-across for the health assessment is performed with HMWPE having a backbone chain length of 7 carbons or greater.
- Structural similarity - the substance without data possesses small incremental structural differences from the reference substance(s) or the difference between the two will not affect the property sufficiently that it cannot be accurately predicted.

For PEs in general, read-across can be applied across increasing/decreasing carbon (C) numbers in the alkyl side-chains. For example, data for dinonyl (di-C9) phthalate and a diundecyl (di-C11) phthalate might be used to read-across to a didecyl (di-C10) phthalate or a phthalate diester with constituents that contain combinations of C9 to C11 alkyl groups. For purposes of discussion, the following general abbreviations will be used in this document to refer to

PE members of this category:

- Di-phC10 PE (CAS No 53306-54-0)
- Di-C7-9 PE (CAS No 68515-41-3)
- Di-C11 PE (CAS No 3648-20-2 or 85507-79-5)
- Di-C9-11 PE (CAS No 68515-43-5)
- Di-C13 PE (CAS No 68515-47-9 or 119-06-2)

Human Health

Data are not specifically available on the toxicokinetics, metabolism, or distribution of the HMWPE covered under this category. However, data developed for DINP are considered to be representative, in a qualitative point of view, of other HMWPE. When orally administered to rodents, DINP is rapidly metabolized in the gastrointestinal tract to the corresponding monoester (MINP), absorbed and excreted, primarily in the urine. Shortly after administration, it is found primarily in liver and kidneys, but it does not persist or accumulate in any organ or tissue. It is very poorly absorbed from the skin, but once absorbed it behaves in the same way as the orally administered substance. The results of these rodent studies contrast with data from studies involving humans or other primates, which indicate low absorption at low oral doses and even more limited total absorption at high doses. Indeed primates appear to be less efficient at metabolizing phthalates to the corresponding monoester, and at high doses absorption of monoester by primates is saturated. One reason for this difference is that there are differing hydrolysis rates for the phthalates between primates and rodents. Consequently, less HMWPE is likely to be absorbed in humans than in rodents.

HMWPE have a low order of acute toxicity by the inhalation, dermal, intraperitoneal and oral routes of exposure. Members of the HMWPE Category are not irritating to the skin or eyes (only slight conjunctival irritation for CAS RN 68515-47-9), neither are they skin sensitizers (Maximization Test or comparable, or Buehler Method). Although some data for these endpoints are older and the peer reviewed publications may not include all desirable methodology, the weight of evidence is consistent.

The primary findings in the repeated dose rat studies were in the liver and kidney and to a lesser degree in the thyroid. Effects to the liver, besides some minor and probably adaptative effects, are indicative of peroxisomal proliferation, including increased PCoA, liver weights, and liver hypertrophy and are not relevant for humans. Indeed, it has been shown that these effects are mediated through the peroxisome proliferation-activated receptor alpha (PPARα) and that levels of PPARα are much higher in rodents than humans. Thus, one would expect humans to be substantially less responsive than rodents to peroxisome proliferating agents. Empirical evidence for this hypothesis has been provided by studies in primates in which repeated administration of DINP had no effects on liver, kidney or testicular parameters, including peroxisome proliferation. The kidney effects were a result of a dose-dependent α-2μ-globulin nephropathy. Such effects are sex- and species-specific to male rats and also are not relevant to humans. The relevance of sporadically observed increased kidney weights in female rats is unclear. Thyroid effects are likely to be a compensatory effect associated with the peroxisomal proliferation in the liver. The results were consistent for all members of the Category, with NOAEL ranging between 10 and 282 mg/kg/day. It should be noted that the 10 mg/kg/day value comes from an OECD 422 study, where rats were dosed for 45 days and the effect observed at 50 mg/kg/day was liver weight increase. This is likely to be related to peroxisome proliferation. The spread in this data is driven by the dose level selection in the various tests. All the NOAELs are driven by liver and/or kidney (common) effects.

HMWPE Category members have been tested in the Ames reverse mutation assay using *Salmonella typhimurium* and all were non-mutagenic with and without metabolic activation. Similarly, a range of substances covering the majority of the carbon numbers in this category were found to be inactive in the mouse lymphoma tests. Additional testing of di-C13 PE showed that the test substance did not induce either structural chromosomal aberrations or polyploidy in CHL cells up to the limit concentration of 4.75 mg/ml, in the absence or presence of an exogenous metabolic activation system. These substances are non-genotoxic based on the negative genotoxicity data for the category as a whole. Although some data for these endpoints are older and the peer reviewed publications may not include all desirable methodology, the weight of evidence is consistent.

Although the HMWPE have not been tested for carcinogenic properties (i.e. chronic toxicity or bioassay studies), previous experience with a wide range of phthalates suggests that high doses might produce liver changes in rodents, but these are not relevant to humans and not indicative of a potential human risk. Three chronic toxicity/carcinogenicity studies of DINP have been conducted; two in rats and one in the mouse. In the rat studies, the major findings were liver and kidney changes principally related to the induction of peroxisome proliferation. There was an increase in liver tumors in both male and female rats and also a small increase in kidney tumors in the male rats. Both of these tumors are considered to be rat specific and without relevance to humans. In the mouse study, there were liver tumors as well, also the consequence of peroxisomal proliferation, but no tumors of other types.

Although not all members of the category have been tested for reproductive toxicity, (di-phC10 PE, di-C11 PE, or di-C13 PE - CAS No 68515-47-9), there are data for the lower (di-C7-9 PE), intermediate (di-C9-11 PE) and higher (di-C13 PE - CAS No 119-06-2) molecular weight representatives that have shown no significant reproductive toxicity at doses up to 500 mg/kg/day or 250 mg/kg/day (di-C13 PE). Effects included transiently decreased body weights or slightly decreased ovary and epididymidal weights. These effects are minor and are not directly related to reproductive toxicity. Furthermore, category members di-C7-9 PE and di-C9-11 PE have been recently shown not to be associated with detectable reproductive effects and do not affect fertility, similarly to DINP and DIDP.

Data from the developmental toxicity tests for the HMWPE conducted in rats, on di-phC10, di-C7-9, di-C9-11, and di-C13 PEs, have shown minimal maternal toxicity, at doses up to 1,000 mg/kg/day (limit dose) or 250 mg/kg/day (in di-C13 PE). Either no effects were produced or the effects were associated with decreased food consumption and body weight loss in dams. Only the di-phC10 PE showed maternal toxicity at the limit dose and associated effects of resorptions, decreased litter size, or fetal survival associated with the above two symptoms of maternal toxicity. In the two-generation study on DIDP, a decrease in offspring survival, more marked in F2, was observed. In the di C13 PE (CAS RN 119-06-2) 1 generation study (F1 generation) a decrease in survival indices was observed leading to a NOAEL of 50 mg/kg/day for offspring rats whereas NOAELs for parental rats were 250 mg/kg. These may be considered related to developmental effects. No such changes were seen in either generation of the separate studies on di-C7-9 PE and di-C9-11 PE; these results are consistent with results from DIDP studies.

However, none of the HMWPE substances tested produced developmental effects. Increased frequencies of developmental variants including dilated renal pelvis and supernumerary lumbar ribs were produced in the studies on di-C7-9 PE and di-C9-11 PE, but are common findings in rats. Although not all members of the HMWPE Category have been tested for developmental toxicity, there are data for the lower (di-phC10 and di-C7-9), intermediate (di-C9-11) and higher (di-C13) molecular weight representatives. Like DINP and DIDP, they have shown no significant developmental toxicity. It is reasonable to conclude that other members of the category would behave similarly, as shown by the weight of evidence. Thus, it can be concluded that this category of HMWPE induces no biologically significant developmental effects in rodents.

In conclusion, as demonstrated in the SIAR (sections 3.1.2 to 3.1.8), the weight of evidence shows that members of the HMWPE Category have a low order of acute and subchronic toxicity. They are not irritating to the skin or eyes. They are not skin sensitizers. They are not mutagenic. No or only minimal developmental toxicity and no adverse effects on reproductive capability have been observed in rodent studies. Thus, there is minimal concern about those PEs resulting in reproductive toxicity in humans.Although not tested for carcinogenicity, the members of this category do not show the potential for producing genetic effects. Also, the same mechanism of action through peroxisome proliferation can be anticipated for induction of liver tumors in rodents, and this is presumed not to be relevant to humans.

The results were consistent for all members of HMWPE Category in all endpoints and the toxicity has been well characterized. No further studies are proposed.

Environment

Members of the HMWPE Category are liquid at 25°C. Most of their physico-chemical properties were obtained by calculation using chemical structures that best characterize the range of constituent chemicals. They demonstrate relatively similar properties or progressive change across a range of values with melting point ranging from -48°C to -9°C, boiling point ranging from 398°C to 501°C (at 1,013 hPa), density ranging from 0.950g/cm^3 to 0.965 g/cm^3, vapour pressure ranging from 3.63E-10 hPa to 9.33E10-7 hPa at 25°C, water solubility values less than 0.0001 mg/l, and log P_{ow} values cited as greater than 6 and ranging up to 12.1.

Results of distribution modeling, using a Mackay Level I model, suggest that members of the HMWPE Category will partition primarily to the soil compartment (approximately 98%) with a small amount partitioning to sediment (approximately 2%). Volatilization to air from aqueous and terrestrial habitats will be negligible because category members have low vapor pressure (<9.33E-7 hPa at 25°C). However, the small fraction that may partition to air has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals with calculated degradation half-lives ranging from approximately 4 to 7 hours depending on hydroxyl radical concentration. Aqueous photolysis and hydrolysis will not contribute to the transformation of phthalate esters in aquatic environments because they are poorly or not susceptible to these reactions. Hydrolysis half-lives of >3 years are estimated for category members.

Members of the HMWPE Category have the potential to biodegrade from 12.8% to 75% biodegradation within 28 days, in ready biodegradability tests. Members of the category, as well as DIDP, have not been shown to be readily biodegradable. Although the two highest molecular weight members of this category, di-C13 PEs with CAS RN 119-06-2 and 68515-47-9, exhibited lower relative extents of biodegradability at 28 days when compared to the other category members, the extant database for these substances show that they can be biodegraded to levels similar to the other lower molecular weight members of this category over an extended test duration (56 days). Data for DINP show that it is readily biodegradable within 28 days. Additionally, studies show that HMWPEs do not inhibit microbial respiration in terrestrial and sewage systems. Category members are expected to sorb to organic matter in soil, sediment, and wastewater solids based on calculated log K_{oc} values that range between 4.5 and 7.7.

The acute and chronic aquatic toxicity of HMWPEs has been evaluated using numerous species. These data clearly show that category members do not exhibit acute and chronic aquatic toxicity at or below their maximum attainable water solubility. The solubility of these substances is equal to or less than 0.017 mg/L. As such, aqueous exposure to these substances will be very limited.

Concerning terrestrial environments, the compartment of primary interest as indicated by partitioning data, studies on members of the HMWPE Category are not available. However, they are not expected to exhibit toxicity based on results from earthworm studies for an analog substance, DIDP, which was applied at a concentration as high as 7,994 mg/kg soil, dry weight. The two lower molecular weight category members, di-C7-9 PE and di-C9-11 PE, may cause effects in plants at very high concentrations, greater than 8,000 mg/kg soil, dry weight, based on data for DINP, which contains constituents that can be found in the two category members. Results from sediment toxicity studies with two freshwater invertebrates that showed no effects at relatively high concentrations (up to 2,900 mg/kg sediment, dry weight) suggest that category members will not produce toxicity to sediment invertebrates. Although the phthalate esters tested, DINP, DIDP, and a di-C7-11 PE, do not belong to the HMWPE Category, select category member constituents have overlapping carbon number ranges and similar structures. Finally, it has been demonstrated that HMWPEs have a low potential to bioaccumulate in aquatic species, demonstrated by a food web study on DINP, and bioconcentration studies on DINP, DiC11-PE and di-C13 PE. Metabolic transformation is the most likely reason why these substances exhibit decreasing concentrations from lower to higher trophic levels.

Exposure

Estimated European production is approximately 60 to 100k tonnes per year (European Council for Plasticisers and Intermediates - personal communication). This is likely to represent a third of world production.

HMWPEs are used primarily as industrial chemicals associated with polymers, mainly as additives to impart flexibility in polyvinyl chloride (PVC) resins, but are also used as synthetic base stocks for lubricating oils. Polymer

applications can be divided into PVC-related uses and uses involving other non-PVC polymers. PVC-containing phthalate ester applications can include wire and cable insulating, furniture and automobile upholstery, flooring, wall coverings, coil coatings, pool liners, roofing membranes, and coated fabrics. Polymer containing phthalate ester applications that are non-PVC based, include thermoplastics, rubbers and selected paints and adhesives. Members of the HMWPE Category are not used for PVC-medical or toy applications. Due to their high viscosity, slow fusion and high costs, members of the HMWPE Category are not preferred for the manufacture of toys.

Essentially all HMWPEs released from their manufacture, which can occur when cleaning manufacturing systems, enter wastewater treatment facilities where they can be biodegraded or sorbed to sewage sludge.

The majority of HMWPEs found in the environment likely come from the slow release of these chemicals from phthalate ester-containing polymer products as a result of weathering processes. Once phthalates are produced and used in various products, emissions can occur during the end-use of these products. Unlike industrial point sources, emissions during product end-use represent a diffuse emission source. In both polymer uses the phthalate ester serves as a plasticiser that enhances the flexibility of the product as a result of the positioning of the phthalate ester molecules between the polymer chains. However, since the phthalate ester molecules are not covalently bound to the polymer matrix, user or consumer exposure, or migration and subsequent release to the environment may occur. Since most HMWPEs are sandwiched within a polymer matrix, emissions are retarded during the life of the polymer product.

Exposure to HMWPEs may occur at workplaces where they are manufactured. Based on physical properties, the primary workplace exposure in production activities would be dermal and there may be a potential for formation of aerosols during some applications. However, HMWPEs are handled only in industrial manufacturing facilities and the majority of the applications involve incorporation of the phthalate ester into a matrix. Therefore, minimal consumer exposure is foreseen, since the consumer is only indirectly exposed through the use of products, which may contain HMWPEs and uptake is expected to be low.

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

The chemicals in this category are currently of low priority for further work because of their low hazard profile.