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Alternatives to classified phthalates in medical devices

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Alternatives to classified phthalates in medical devices

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Preface

The use of phthalates, particularly DEHP, BBP, DBP and DIBP, in consumer products with known human exposure, has been a focus point the last decades due to their reproductive and endocrine disrupting effects evidenced on certain animals. Based on the harmonised classification as toxic for reproduction and on the wide dispersive use, these four phthalates have been placed on the authorisation list of Annex XIV under REACH for which future uses have to be approved[1].

Attention has been put on alternatives to these phthalates, especially in the area of medical devices; of particular concern is exposure to sensitive user groups, i.e. pregnant, neonatal and small children. In 2003, the Danish EPA identified a number of alternatives that might be substitutes for DEHP in PVC applications used in medical devices. This evaluation was based on technical aspects. In 2010, the Danish EPA evaluated alternatives to phthalates in terms of toxicological and ecotoxicological effects, but a number of data gaps was identified.

The overall purpose of this project is to make an update on the toxicological and ecotoxicological effects of a number of alternatives. This will be based on the available data, primarily retrieved from the registration dossiers under REACH submitted by the industry, but also based on supplementary data from producers of the alternatives and of medical devices.

The outcome of the project will be a list of alternatives, each described by a data sheet with key information on the toxicological and ecotoxicological profiles. This list may help guide industry for substitution of DEHP, BBP, DBP, and DIBP.

This project “Alternatives to phthalates in medical devices” was carried out during the period from July 2013 to December 2013.

The project was implemented by DHI by a project team consisting of Dorthe Nørgaard Andersen (project manager), Brian Svend Nielsen, Estelle Giovalle, Morten Bjergstrøm and Poul Bo Larsen.

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[1] Annex XIV REACH regulation.

Summary and conclusions

Phthalates are widely used as plasticisers in PVC formulations. Phthalates are in focus because of their reproductive and endocrine disrupting effects. A number of phthalates, including the four phthalates DEHP, BBP, DBP, and DIBP, are listed on the Candidate List under REACH, due to the classification as toxic for reproduction and the wide dispersive use.

In spite of the extensive work carried out over the past 10-20 years on alternatives to phthalates, the environmental and health effects of the alternatives still need to be reviewed. This also includes alternative substances or groups of substances that can replace the use of phthalates. The objective of this project is to create an overview of the human and environmental effects of potential alternative plasticisers in order to help the industry and importers to select appropriate alternatives for the most problematic phthalates (at present the four phthalates DEHP, BBP, DBP and DIBP).

The harmonised classifications of the 4 phthalates are described below.
DEHP: Repr. 1B, H360FD (May damage fertility, May damage the unborn child)
BBP: Repr. 1B, H360Df (Suspected of damaging fertility, May damage the unborn child)
DBP: Repr. 1B, H360Df (Suspected of damaging fertility, May damage the unborn child)
DIBP: Repr. 1B, H360Df (Suspected of damaging fertility, May damage the unborn child)

Based on previous market experience in the area of medical devices, a list of alternative plasticisers was produced. This list was circulated in Europe to different producers of alternatives, producers of different medical devices using these alternatives, different organisations involved, and the plastic industry for commenting. Based on the feedback from these, a final list of 10 alternatives was generated for further evaluation in terms of human health and environmental toxicity.

The 10 identified alternative plasticisers were:

- ASE - Sulfonic acids, C10-21-alkane, Ph esters (CAS No 91082-17-6)
- ATBC - tributyl O-acetylcitrate (CAS No 77-90-7)
- BTHC - butyl trihexyl citrate (CAS No 82469-79-2)
- COMGHA - glycerides, castor-oil-mono-, hydrogenated, acetates (CAS No 736150-63-3)
- DEHT - bis(2-ethylhexyl) terephthalate (CAS No 6422-86-2)
- DINA - diisononyl adipate (CAS No 33703-08-1)
- DINCH - Diisononyl cyclohexanedicarboxylate (CAS No 166412-78-8)
- DOA/DEHA - Bis(2-Ethylhexyl) Adipate (CAS No 103-23-1)
- ESBO - Epoxidized soybean oil (CAS No 8013-07-8)
- TOTM/TEHTM - trioctyl trimellitate/tri-(2-ethylhexyl)- trimellitate) (CAS No 3319-31-1)

Publicly available data on the 10 alternative plasticisers were extracted from the latest REACH registration dossiers (2013) from ECHA's homepage. These data are considered to be the most updated information for these substances. From these data, human health and environmental profiles for each of the alternative substances were elaborated in the form of datasheets. For each of the (eco)toxicity endpoints, key studies and supplementary studies (if evaluated to be needed in the overall conclusion) with Klimisch scores of 1 and 2 were considered. The Klimisch scores of 1 and 2 indicate that the data were of good quality, usually test data from studies performed in accordance with internationally recognised test guidelines (or similar to) and GLP.

REACH registration dossiers were available for most of the alternative substances with varying degree of information. However, for BTHC (CAS 82469-79-2) no registration dossier could be retrieved, and data were therefore extracted from previous evaluations and a safety data sheet supplied from the producer. For DINA (CAS 33703-08-1) read-across was used for most endpoints. In terms of DINCH, the key studies in the registration dossier are presented with few details; supporting information has therefore been retrieved from other sources (NICNAS, GreenScreen Assessment from Toxservices).

Conclusions

Evaluations of the 10 alternative plasticisers have been based on the study summaries and conclusions drawn in the registration dossiers by the registrants. Available data on the human health and environmental properties of the selected alternatives have been elaborated, reviewed and reported in datasheets. Summary tables with key information have been established and compared with DEHP in terms of NOAELs, critical effect and the DNEL-values (Derived No Effect Level) elaborated by the registrant. It has to be emphasised that all conclusions drawn in the registration dossiers are the responsibility of the registrants, and the results and conclusions drawn from these have therefore only been referenced in this evaluation. Thus, this evaluation should be seen as a screening of the available data rather than an in-depth evaluation.

In terms of the human health hazard profiles, it can be noted that the DNELs (general population) derived by the registrants for the alternative plasticisers are all higher in comparison with the DNELs (general population) for DEHP. Further, it is noted that the alternatives did not have the same type of toxicological profile as seen for DEHP in terms of reproduction and development. The exception is DOA which is suspected of having effects on the male reproductive system based on the structural similarities and metabolism with DEHP.

For the alternatives COMGHA, DEHT and DINCH, a data set fulfilling the requirements for a high tonnage registration (Annex X) in relation with reproduction and development was available, i.e. a reproductive toxicity study over two generations (OECD 416). For five of the alternatives (ASE, BTHC, DINA, DOA and ESBO), reproductive toxicity over one generation (OPECD 415) has been investigated. For ATBC, no information on reproductive toxicity could be retrieved from the registration, and for TOTM the only identified data set from the registration dossier was from a reproduction and developmental toxicity screening study (OECD 421). For TOTM, supplementary information on reproduction was available from a 90-day toxicity study and from a mechanistic transcriptional profiling study.

In relation to a possible endocrine activity of the alternatives, more data is needed to fully explore these properties. Only data on COMGHA, DEHT, DINCH, DOA and TOTM were available with varying levels of information and type of endpoints investigated. For these, a clear and definite conclusion on a possible endocrine disrupting effect was not possible, as the underlying mechanism of endocrine disrupting effects has not been fully investigated. It is however noted that the available data for COMGHA, DEHT and DINCH do not indicate a need for further investigations.

A discussion is on-going in relation to DINCH due to potentially relevant effects in reproductive/developmental and thyroid endpoints. It is noted that this has been argued from the producer not to be relevant effects, and further supported by authorities (NICNAS, EFSA and SCENIHR). DOA (CAS No 103-23-1) raises some concern for reproductive toxicity and developmental toxicity (foetotoxicity, i.e. reduced ossification and increased incidences of visceral variants) and recently has been listed on the CORAP list[2] due to human health consideration based

[2] Justification for the selection of a candidate CoRAP substance http://echa.europa.eu/documents/10162/2bc79569-1f0d-4c35-ad6e-29c4c7656298

on the structural similarities and metabolism with DEHP. Further, DOA shows some indications of endocrine activity, i.e. affected thyroid hormone function[3].

In conclusion, 10 alternatives to DEHP have been evaluated in terms of their human health hazard profiles based on the available data sets, and these are to various degrees considered to be relevant alternatives to DEHP in terms of human health hazards. Although far from tested to the same degree as e.g. DEHP (with respect to reproductive toxicity and endocrine disruption), the substances COMGHA, DEHT and DINCH may be seen as the most promising alternatives, as these substances have an extended data set (complying to Annex X data requirements, i.e. a two-generation reproduction study) without indicating specific concern for reproductive toxicity or endocrine activity. It has to be emphasised that this evaluation primarily is based on the available data from the substances' REACH registration dossiers, and that for most substances a general lack of information on reproductive toxicity and potential endocrine disrupting effects is missing.

In terms of the environmental hazard profiles, it seems that the alternative plasticisers show similarities to DEHP. COMGHA, DEHT, DINA and DOA are assessed to be readily biodegradable, whereas ASE, ATBC, DINCH, and TOTH are assessed to be inherently biodegradable. It is noted that TOTM (CAS No 3319-31-1) has been listed on the CORAP list for environmental concerns/suspicion of PBT properties. Information from the producer though rejects this concern. The alternatives appear not to have any acute ecotoxicological effects on algae, crustaceans and fish. Only one of the alternatives, ATBC, was screened to be bioavailable (based on QSAR prediction) indicating a potential for being biologically active. No toxicological data were found which either could support or reject the hypothesis that ATBC may cause endocrine disrupting effects. QSAR prediction of bioavailability was not calculated for COMGHA, but toxicological data show that COMGHA causes no antiandrogen effects.

In conclusion, considering the similar environmental effects profiles to DEHP, the evaluated alternative plasticisers may be used as substitutes for DEHP based on the environmental hazard profile.

Overall, the report identified 10 potential alternatives to DEHP in medical devices. The alternatives have been studied for their inherent environmental and health properties. Most of the considered alternatives show a better toxicological profile than DEHP, and are thus preferable to DEHP. However, data are lacking for a few of the alternatives, before a toxicological assessment can be carried out.

All 10 potential alternatives are used today as plasticisers in medical devices. However, it is very important to emphasise that the report does not assess whether the alternatives are technically applicable in all types of medical devices, which today are plasticised with DEHP. It is up to the manufacturers of the medical devices to resolve whether a DEHP-substitution could be achieved without compromising patient safety.

In addition, the report does not comment specifically on whether and to what extent classified phthalates in all medical devices can actually be replaced, so the products still have the necessary specific properties to be used in disease treatment. This is up to the professional and technical assessment of the companies.

[3] Analysis of Alternatives (non-confidential report), Hazard and risk evaluation of DEHP alternatives prepared on behalf of the DEHP authorization task force (ATF), June 2013 – ARKEMA, France

Resumé og konklusion

Ftalater anvendes i vid udstrækning som blødgørere i PVC-plastprodukter. Der er imidlertid fokus på udvalgte ftalater på grund af stoffernes hormonforstyrrende effekter og deres skadelige effekter på fosterudvikling og fertilitet. De fire ftalater DEHP, BBP, DBP og DIBP er således anført på godkendelseslisten under REACH på grund af klassificering som reproduktionstoksisk og udbredt anvendelse.

I forbindelse med det omfattende substitutionsarbejde, der er udført i løbet af de sidste 10-20 år for at opnå alternativer til ftalater, er det nødvendigt at undersøge alternativernes miljø- og sundhedsmæssige effekter. Formålet med dette projekt er at skabe et overblik over de sundheds- og miljømæssige effekter af potentielle alternative blødgørere for at hjælpe industrien og importørerne til at udvælge mulige alternativer for de mest problematiske ftalater (på nuværende tidspunkt de fire ftalater DEHP, BBP, DBP og DIBP).

De 4 ftalater, for hvilke der søges alternativer, er klassificeret med følgende harmoniserede klassificering:
DEHP: Repr. 1B, H360FD (Kan skade forplantningsevnen, Kan skade det ufødte barn)
BBP: Repr. 1B, H360Df (Mistænkt for at skade forplantningsevnen, Kan skade det ufødte barn)
DBP: Repr. 1B, H360Df (Mistænkt for at skade forplantningsevnen, Kan skade det ufødte barn)
DIBP: Repr. 1B, H360Df (Mistænkt for at skade forplantningsevnen, Kan skade det ufødte barn)

Baseret på tidligere erfaringer fra markedet inden for medicinsk udstyr er der blevet lavet en liste over alternative blødgørere. Denne liste har været rundsendt i Europa til forskellige producenter af alternativer, producenter af forskelligt medicinsk udstyr, forskellige involverede organisationer og plastindustrien. Baseret på tilbagemeldinger fra disse blev der lavet en endelig liste over 10 alternativer til yderligere evaluering med hensyn til sundheds- og miljøeffekter.

De 10 identificerede alternative blødgørere omfatter:

- ASE - sulfonsyrer, -C10-21-alkan-, -phenylestere (CAS Nr. 91082-17-6)
- ATBC - tributyl-O-acetylcitrat (CAS Nr. 77-90-7)
- BTHC - butyl trihexyl citrat (CAS Nr. 82469-79-2)
- COMGHA - glycerider, castor-olie-mono-, hydrogeneret, acetate (CAS Nr. 736150-63-3)
- DEHT - bis(2-ethylhexyl)terephthalat (CAS Nr. 6422-86-2)
- DINA - diisononyladipat (CAS Nr. 33703-08-1)
- DINCH - Diisononyl cyclohexanedicarboxylate (CAS Nr. 166412-78-8)
- DOA/DEHA - bis(2-ethylhexyl)adipate (CAS Nr. 103-23-1)
- ESBO - sojaolie,-epoxideret (CAS Nr. 8013-07-8)
- TOTM/TEHTM - tris(2-ethylhexyl)benzen-1,2,4-tricarboxylat (CAS Nr 3319-31-1)

For at opnå sundheds- og miljødata på disse stoffer blev der i dette projekt indhentet information for stofferne i de offentligt tilgængelige data i REACH registreringsdossiererne (2013) fra ECHAs hjemmeside. Som følge af registranternes oplysningspligt burde disse data omfatte de mest opdaterede oplysninger om stofferne. Ud fra disse data blev der udarbejdet sundheds- og miljømæssige profiler for hvert af de alternative stoffer i form af datablade. For hvert af de (øko)toksiske effektområder blev de mest centrale undersøgelser med en Klimisch score på 1 og 2 inddraget. Klimisch scoren på 1 og 2 viser, at data var af god kvalitet, sædvanligvis testdata fra studier udført i overensstemmelse med internationalt anerkendte retningslinjer for testning (eller

lignende) og GLP. Evt. supplerende information (fx særlige ekspertvurderinger) blev inddraget, hvis det vurderedes at være nødvendigt i den overordnede konklusion.

Registreringsdossierer var tilgængelige for de fleste af alternativerne med varierende grad af oplysninger. Men for BTHC (CAS 82469-79-2) kunne der ikke hentes noget registreringsdossier, og data blev derfor trukket fra tidligere evalueringer og et sikkerhedsdatablad fra producenten.

Konklusioner

Evalueringerne af de 10 alternative blødgørere er baseret på registranternes resume af undersøgelserne og deres konklusioner i registreringsdossierne. De tilgængelige data for alternativernes sundheds- og miljømæssige egenskaber er blevet bedømt og rapporteret i datablade. Der er lavet oversigtstabeller med de centrale oplysninger, og disse er blevet sammenlignet med DEHP med hensyn til NOAEL- (kritisk effekt) og DNEL-værdier (Derived No Effect Level) udarbejdet af registranten. Det skal understreges, at alle konklusioner fra registreringsdossierne er registrantens ansvar, og at alle resultater og konklusioner beskrevet i denne rapport er refereret fra registreringsdossierne. Resultaterne i denne rapport er derfor baseret på en screening af de tilgængelige data, og ikke på en dybdegående evaluering af originaldata.

Med hensyn til sundhedsprofiler kan det bemærkes, at alle DNEL værdier, der er afledt af registranterne for de alternative blødgørere, er højere sammenlignet med DNEL–værdien for DEHP. Endvidere skal det bemærkes, at alternativerne ikke har samme type toksikologiske profil, som ses for DEHP med hensyn til reproduktion og udvikling. Undtagelsen er DOA som pga. metabolisme og strukturel sammenlignelighed med DEHP er mistænkt for at have tilsvarende skadelige effekter på den mandlige reproduktion.

I forhold til mulige påvirkninger af hormonsystemet er der behov for flere data til fuldt ud at undersøge disse egenskaber. Denne type data var kun tilgængelige i varierende omfang for stofferne COMGHA, DEHT, DINCH, DOA og TOTM. For disse er en endelig konklusion på eventuel hormonforstyrrende potentiale således ikke mulig, da der fortsat savnes nogle undersøgelser for fuldt at afklare dette. Det skal dog understreges, at de tilgængelige data for COMGHA, DEHT og DINCH ikke giver anledning til mistanke om hormonforstyrrende effekter.

For DINCH er der en igangværende diskussion vedrørende effekter i forhold til reproduktion og udvikling, herunder effekter på thyroidea. Det skal bemærkes, at dette er blevet fremført fra producenten ikke at være relevante effekter, og det understøttes yderligere af flere ekspertgrupper (NICNAS, EFSA og SCENIHR). Desuden giver DOA (CAS nr. 103-23-1) anledning til en vis bekymring for effekter på reproduktion, og DOA er for nylig blevet anført på CORAP-listen for at opnå yderligere klarhed om evt. sundhedsskadelige effekter.

Ud fra den foreliggende screening af data må stofferne COMGHA, DEHT og DINCH anses for at være de mest lovende alternativer, da disse stoffer har udvidede datasæt (opfylder datakravene i Bilag X), samtidig med at data ikke konkret giver anledning til mistanke om skadelige effekter på fertilitet og udvikling. Det skal understreges, at denne evaluering primært er baseret på tilgængelige data om stofferne i REACH registreringsdossierer.

Med hensyn til miljøprofilerne anses de alternative blødgørere at udvise flere ligheder med DEHP. COMGHA, DEHT, DINA og DOA vurderes at være let bionedbrydelige, mens ASE, ATBC, DINCH og TOTH vurderes at være potentielt bionedbrydelig. Det skal bemærkes, at TOTM (CAS nr. 3319-31-1) er anført på CORAP-listen på grund af miljøhensyn/mistanke om PBT-egenskaber. Oplysninger fra producenten afviser dog denne mistanke baseret på evaluering fra myndighedernes side, og yderligere studier er igangsat for at undersøge dette nærmere.

Generelt synes alternativerne ikke at have nogen akutte økotoksikologiske effekter på alger, krebsdyr og fisk.

Kun et af alternativerne, ATBC, blev screenet som værende biotilgængeligt (baseret på QSAR forudsigelse), hvilket indikerer et potentiale som værende biologisk aktiv i miljøet. Der er ikke fundet nogen toksikologiske data, som enten kan understøtte eller afvise hypotesen om, at ATBC kan medføre hormonforstyrrende effekter. Der er ikke beregnet en QSAR forudsigelse af biotilgængelighed for COMGHA, men toksikologiske data viser, at COMGHA ikke medfører antiandrogene effekter.

Overordnet set er der i rapporten identificeret 10 potentielle alternativer til DEHP i medicinsk udstyr. Alternativerne er undersøgt for deres iboende miljø- (og sundhedsmæssige) egenskaber. Den overvejende del af de undersøgte alternativer viser en bedre toksikologisk profil end DEHP og er således at foretrække fremfor DEHP. Et par af alternativerne mangler dog data, førend en toksikologisk vurdering lader sig foretage. Ud fra den foreliggende screening af data må stofferne COMGHA, DEHT og DINCH anses for at være de mest lovende alternativer, da disse stoffer har udvidede datasæt (opfylder datakravene i Bilag X), samtidig med at data ikke konkret giver anledning til mistanke om skadelige effekter på fertilitet og udvikling.

Afslutningsvis kan det nævnes, at alle 10 potentielle alternativer i dag anvendes som blødgørere i medicinsk udstyr. Hvad der imidlertid er meget vigtigt at få understreget er, at rapporten ikke vurderer, om alternativerne teknisk set er anvendelige i alle de typer af medicinsk udstyr, som i dag er blødgjort med DEHP. Det er i den forbindelse op til producenterne af det medicinske udstyr at få afgjort, om en DEHP-substitution kan gennemføres, uden at anvendeligheden af det medicinske udstyr og patientsikkerheden kompromitteres.

Derudover er der i rapporten ikke taget konkret stilling til, om og i hvilket omfang klassificerede ftalater faktisk kan erstattes i alt medicinsk udstyr, uden at produkterne mister de nødvendige specifikke egenskaber, der er nødvendige for anvendelse i sygdomsbehandlingen. Dette beror på virksomhedernes faglige og tekniske vurderinger.

1. Introduction

Phthalates are widely used as plasticisers in PVC materials, including the area of medical devices (blood bags, catheters, tubing, bags for ostomy). The use of phthalates in PVC applications has gained a lot of attention because of its known reproductive and endocrine disrupting effects as shown in series of experimental animal studies, where especially the large data base on DEHP has gained a lot of attention. DEHP is used as a plasticiser in many different product groups, including the area of medical devices. The key concern in relation to DEHP is migration from plasticised materials to the user of the medical device. Based on the toxicological effects of DEHP and a possible human exposure, through contact with skin, tissue and blood, the greatest concern for users of medical devices plasticised with DEHP is the sensitive subpopulations (neonatal, children, pregnant).

In general, substitution of phthalates (DEHP) used in medical devices has gained a lot of attention both nationally and internationally, and therefore business trade organisations in Denmark together with national authorities are focusing on identifying relevant alternative plasticisers to be used as a replacement for DEHP.

This project is made in collaboration between DHI, the Danish EPA, the Danish Health and Medicines Authority, and the Danish PVC Council focusing on identifying a number of useable alternatives to DEHP in medical devices, and further to make an assessment of the toxicological and ecotoxicological effects of these. The outcome of the project is a list of alternative plasticisers to DEHP in medical devices describing key parameters, and a datasheet for each of the alternatives. This list is thought as a “tool” for manufacturers of medical devices to potentially substitute DEHP.

The results of this report will be presented at a planned workshop in 2014.

2. Medical devices

2.1 Classification

The purpose of reducing the use of phthalates in medical devices is to reduce human exposure to these substances, as some phthalates are classified as toxic to reproduction. In Denmark, it has been decided to introduce a ban of four phthalates (DEHP, DBP, BBP and DIBP) in consumer products for indoor use, and also for products with plasticised parts that may come into contact with skin or mucous membranes.

For certain types of medical devices, it is crucial for the functionality of the products that they are extremely soft and flexible, e.g. feeding tubes and other types of devices. In some cases, such devices contain phthalates as plasticisers. According to our information, DEHP is the most frequently used type of plasticiser worldwide in medical devices.

In general, the benefits of being able to offer the most efficient and optimal treatment of patients outweigh the potential risk from the presence of phthalates in the medical devices. That being said however, it is important to take initiatives to ensure a continued reduction of the use of classified phthalates in medical devices whenever possible without compromising patient safety, and to constantly work to minimise the use of classified phthalates in general.

In the EU, for certain types of medical devices the use of phthalates with a harmonised classification as CMR according to CLP[4] must be labelled. The request for labelling applies to medical devices for handling/administration of medicines or body fluids, e.g. intravenous tubing and bags, catheters, nasogastric tubes, dialysis bags, and tubing, blood bags, and transfusion tubing, air tubes, and tubes for parenteral nutrition[5].

In general, in the EU a medical device is categorised based on the proposed use and exposure[6]. The following categories are used depending on the risk, i.e. ranging from low to high risk:

Class I, Class IIa, Class IIb and Class III

The classification depends on rules that involve the medical device's duration of body contact, invasive character, use of an energy source, effect on the central circulation or nervous system, diagnostic impact, or incorporation of a medicinal product.

Certified medical devices should have the CE mark on the packaging and insert leaflets. This is issued by the manufacturer himself, but for products in Class IIa, IIb or III, it must be verified by a notifying body.

[4] Classification and labelling of DEHP as Category 1B reproductive toxicant for both fertility and developmental effects in accordance to CLP regulation (EC/1272/2008).
[5] Council Directive 93/42/EEC, amended by Directive 2007/47/EEC
[6] Council Directive 93/42/EEC, amended by Directive 2007/47/EEC

2.2 Formulation of PVC with plasticiser

A large number of different plasticisers are used in formulations with PVC, but phthalates are the most commonly used. Phthalates are manufactured by reacting phthalic anhydride with alcohol(s), which range from methanol and ethanol (C1/C2) to tridecyl alcohol (C13), either as a straight chain or with some branching. They are divided into two distinct groups based on the number of carbon atoms in their alcohol chain. High molecular weight (HMW) or high phthalates (e.g. DINP, DIDP, DPHP, DIUP, and DTDP) include those with more than 6 carbons in their backbone, which gives them increased permanency and durability. Low molecular weight (LMW) or low phthalates (e.g. DEHP, DBP, DIBP, and BBP) are those with only 3-6 carbon atoms in their side chains.
Alternative plasticisers are mainly from the following chemical groups:

- **Aliphatic dibasic acid esters**. These types of plasticisers are based on aliphatic dibasic acids with carbon numbers ranging from C5 (glutaric) to C10 (sebacic) and includes adipates (DOA), Sebacates and Azelates.
- **Benzoate esters.** Di-benzoate plasticisers are obtained by direct esterification of benzoic acid with glycols for use primarily in non PVC applications.
- **Citrates.** Citric acid is the starting material for a number of citrate ester plasticisers, such as tributyl citrate, acetyl tributyl citrate (ATBC), triethyl citrate, acetyl triethyl citrate and tri-2-ethylhexyl citrate.
- **Epoxy plasticisers.** Esters containing an epoxy group such as epoxidised soybean oil (ESBO) and epoxidised linseed oil (ELO). They are formed by the oxidation of an olefinic double bond to an oxirane structure.
- **Phosphate Esters.** The principal advantage of phosphate esters is their improved fire retardancy compared to phthalates. Triaryl phosphates and alkyl diaryl phosphates are the two important categories of flame retardant phosphate plasticisers.
- **Polymeric plasticisers**. Polyesters produced from polyhydric alcohols (diols) that have been esterified with dibasic acids, commonly adipic acid, in the presence of monobasic acids or alcohols.
- **Cyclohexane diacids esters.** Di-isononyl cyclohexane dicarboxylate produced by the selective hydrogenation of the aromatic ring in di-isononyl phthalate (DINP), in the presence of a noble catalyst.
- **Terephthalates**. Other commercial isomeric form of phthalates. Terephthalates are esters of tere-phthalic acid. Terephtalates plasticisers include the 1,4 benzenedicarboxilic acid ester sometimes referred to as DEHTP (di-(2ethylhexyl) terephthalate) or DOTP di-octyl terephthalate.
- **Triglyceride plasticisers.** Different types of glycerol esters have been proposed as alternatives to low phthalates, their limited availability and higher costs currently limit their use.
- **Trimellitates.** Produced by the esterification of C7-C10 alcohols with trimellitic anhydride (TMA). Consequently, esters are produced in the ratio of three moles of alcohol to one mole of anhydride. Common esters in this family are Tris-2-ethyhexyl trimellitate (Tri-octyl trimellitate - TOTM), L79TM, an ester of mixed semi-linear C7 and C9 alcohols, and L810TM, an ester of mixed C8 and C10 linear alcohols.
- **Glycerol Acetylated esters.** Made from fully hardened castor oil and acetic acid. Castor oil is extracted from the seeds of the castor oil plant, which is an annual plant grown in India, Brazil and China. The castor oil contains between 85% to 95% ricinoleic acid. The performance of castor oil is improved by modifying its structure (hardening) and replacing the longer chain acids with acetic acid.

In general, PVC formulations contain PVC Resin (Suspension Grade, Paste Grade, and Copolymer), Primary Plasticiser, Secondary Plasticiser, Stabilisers (Heat Stabilisers, Light Stabilisers), Lubricants, Fillers, Pigments and Special Additives.

For PVC Resin, there are 4 types grouped by the polymerisation method, the Suspension Grade PVC, the Emulsion Grade PVC, the Bulk Polymerised PVC, and the Copolymer PVC

The Primary plasticisers make the hard PVC resin softer. Primary plasticisers have good compatibility with PVC resin and can be absorbed in large quantities. The phthalate esters are the most used as primary plasticiser.[7]

Secondary plasticisers are extenders, which when combined with a primary plasticiser will add flexibility to the final product. The majority of secondary plasticisers in use are chlorinated paraffins, which are hydrocarbons chlorinated to a level of 30-70%, typically 52%.

[7] The information in this section has been retrieved from the homepage "Plasticisers and flexible PVC information centre", an initiative of the European Council for Plasticisers and Intermediates (ECPI) http://www.plasticisers.org/

3. List of alternatives

Initially, the list of alternatives (Table 1 below) has been produced based on the results from a report identifying 10 alternatives to phthalates, including DEHP[8]. The data for the 10 alternatives in the report from The Danish EPA have been collected from the industry, relevant databases, and peer reviewed literature. This list was circulated in Europe to different producers of alternatives, producers of different medical devices using these alternatives, different organisations involved, and the plastic industry for commenting. Based on the feedback from these, a suitable list of 10 alternatives (Table 1 below) was generated for further evaluation.

Supplementary information used in Table 1 has been retrieved from the SCENIHR report[9], the RAC risk assessment report[10], the report from the Lowell center for sustainable production[11] and the paper by Chiellini et al.[12]. Furthermore, a publicly available application for authorisation to use DEHP for industrial use in polymer processing to produce PVC articles was consulted at the ECHA homepage[13].

The 10 identified alternatives to DEHP in medical devices were selected based on a number of criteria such as previous market experience, specifically experience in the area of medical devices i.e. blood bags, tubings, etc. for sensitive applications, technical aspects in terms of leaching/migration and volatility, and further technical aspects in terms of performing properties of plasticisation and processing of the polymeric matrix.

Migration of plasticiser from PVC is a matter of concern in terms of consumer exposure, and therefore data on migration from food contact materials and medical devices are crucial for estimating exposure. Migration data have been retrieved from producers of the alternatives combined with data from other sources as mentioned above.

The following 10 alternatives were evaluated in terms of human health and environmental aspects:

- ASE - Sulfonic acids, C10-21-alkane, Ph esters (CAS No 91082-17-6)
- ATBC - tributyl O-acetylcitrate (CAS No 77-90-7)
- BTHC - butyl trihexyl citrate (CAS No 82469-79-2)
- COMGHA - glycerides, castor-oil-mono-, hydrogenated, acetates (CAS No 736150-63-3)
- DEHT - bis(2-ethylhexyl) terephthalate (CAS No 6422-86-2)
- DINA - diisononyl adipate (CAS No 33703-08-1)
- DINCH - Diisononyl cyclohexanedicarboxylate (CAS No 166412-78-8)
- DOA/DEHA - Bis(2-Ethylhexyl) Adipate (CAS No 103-23-1)
- ESBO - Epoxidized soybean oil (CAS No 8013-07-8)
- TOTM/TEHTM - trioctyl trimellitate/tri-(2-ethylhexyl)- trimellitate) (CAS No 3319-31-1)

[8] Identification and assessment of alternatives to selected phthalates, The Danish EPA, Environmental project No. 1341, 2010.
[9] SCENIHR, Opinion on the safety of medical devices containing DEHP or other plasticisers on neonates and other groups possible at risk, 2008.
[10] RAC Background document to the Opinion on the Annex XV dossier proposing restrictions on four phthalates, 2012.
[11] Technical briefing, Phthalates and their alternatives: Health and Environmental concerns, Lowell centre for sustainable production, 2011.
[12] Perspectives on alternatives to phthalate plasticised poly(vinyl chloride) in medical device applications, Progress in polymer sciences 38 (2013) 1067-1088, Chiellini et al, 2013
[13] Analysis of Alternatives (non-confidential report), Hazard and risk evaluation of DEHP alternatives prepared on behalf of the DEHP authorization task force (ATF), June 2013 – ARKEMA, France

Substance	Group of plasticisers	CAS-no	Market and technical experience	Migration data	Conclusion	REACH registration (Tonnage band)
ASE (Sulfonic acids, C10-C18-alkane, phenylesters)	Sulphonates	91082-17-6	A general plasticiser alternative to DEHP. The producer has indicated significant market experience for most traditional DEHP, DBP and BBP uses. PVC compounding ok.	Extraction rate of ASE from PVC resin into water higher compared to DEHP, low migration into ethanol, a higher saponification resistance compared to DEHP.	Primary plasticisers that are technically an alternative to DEHP in medical devices.	10,000 - 100,000 tpa
ATBC (Acetyl tributyl citrate)	Citrates	77-90-7	Significant market experience, an effective alternative plasticiser for DEHP in medical devices PVC compounding ok.	High extractability - migration into aqueous solutions, high volatility, problem in some applications with lipid contact.	Primary plasticisers that are technically an alternative to DEHP in medical devices. Migration could be a problem for specific uses.	1,000 – 10,000 tpa
BTHC (butyl trihexyl citrate)	Citrates	82469-79-2	Used in blood storage bags	ND	Primary plasticisers that are technically an alternative to DEHP in medical devices.	No REACH registration dossier
COMGHA (Glycerides, castor-oil mono-, hydrogenated, acetates)	Castor oil derivatives	736150-63-3	Relative moderate market experience for traditional DEHP uses. Approved for use in food contact materials, used for toys and medical devices (tubing, connectors, dialysis, catheters, fluid bags), PVC compounding ok	High extraction resistance in aqueous and oily solvents, thus low migration potential from medical devices. Low volatility.	Primary plasticisers that are technically an alternative to DEHP in medical devices. COMGHA of natural origin. Low migration potential.	1,000 – 10,000 tpa
DEHT (Di-ethylhexyl-terephthalate)	Terephthalate	6422-86-2	Significant market experience for traditional DEHP uses. Significant use experience in medical devices. Reported as a suitable alternative for some uses of BBP, in applications where both DEHP and BBP could be used. PVC compounding ok	Similar extraction values to DEHP in oil and hexane lower in soapy water. Lower volatility than DEHP. The low temperature flexibility of DEHT in PVC is equal to that of DEHP.	Primary plasticisers that are technically an alternative to DEHP in medical devices. Low migration potential.	10,000 – 100,000 tpa
DINA (Diisononyl	Aliphatic dibasic esters	33703-08-1	DINA has mostly been used for low temperature PVC applications and in PVC film/wrapping. Frequently used alternative	In PVC, DINA has similar hardness and volatility as DEHP, but higher extractability in water and kerosene.	Primary plasticisers that are technically an alternative to DEHP in medical devices. Already used	> 1,000 tpa

Substance	Group of plasticisers	CAS-no	Market and technical experience	Migration data	Conclusion	REACH registration (Tonnage band)
adipate)			in toys, according to surveys. Adipate group representative of DEHP substitutes. PVC compounding ok	In general, adipates show higher extractability (migration) than DEHP.	in medical devices for specific product groups but migration could be a problem.	
DINCH (Di-isononyl-cyclohexane-1,2-Dicarboxylate)	Cyclohexanes	166412-78-8	Most used alternative in PVC applications. Significant market experience in traditional DEHP uses PVC applications. DINCH is suggested as an alternative to DEHP in blood bags tubes and packing for nutrient solutions. PVC compounding ok.	Very low migration rate (3-10 times lower than DEHP in PVC) suitable for sensitive applications (tubes for internal feeding, haemodialysis bags, respiratory tubes, catheters, gloves and breathing masks)	Primary plasticisers that are technically an alternative to DEHP in medical devices. Already used in medical devices for specific product groups.	Tonnage data confidential
DOA (Bis(2-Ethylhexyl) Adipate)	Adipates	103-23-1	Significant market experience among alternatives for normal DEHP applications. DOA used in medical devices in general. PVC compounding ok but exhibit poorer fusion and compatibility with PVC, use in blends with high phthalates.	Relative to phthalates, adipates are more volatile and have higher migration rates	Primary plasticisers that are technically an alternative to DEHP in medical devices. Already used in medical devices for specific product groups.	10,000 - 100,000 tpa
ESBO (Epoxidized soybean oil)	Epoxy esters and epoxidized oils	8013-07-8	Market experience on use in medical devices.	Low volatility	Secondary plasticisers that can be used in conjunction with primary plasticiser.	10,000 – 100,000 tpa
TOTM/TEHTM (Trioctyl trimellitate /Tri-(2-ethylhexyl)-trimellitate)	Trimellates	3319-31-1	Market experience on use in medical devices	Very low migration rate (up to 1000 times lower than DEHP in PVC)	Primary plasticisers that are technically an alternative to DEHP in medical devices. Already used in medical devices for specific product groups	10,000 – 100,000 tpa

TABLE 1
DESCRIPTION OF THE 10 ALTERNATIVE PLASTICISERS IN TERMS OF CHEMICAL GROUP, CAS NO., MARKET AND TECHNICAL EXPERIENCE, DATA ON MIGRATATION AND CONCLUSION. THE DATA HAS BEEN RETRIEVED FROM PRODUCERS AND SUPPLEMENTARY REFERENCES. A LIST OF PRODUCERS AND TRADE NAMES/SYNONYMS OF THE ALTERNATIVES IS SUPPLIED IN APPENDIX 1. THE LAST COLUMN OF THE TABLE DESCRIBES THE REACH REGISTRATION STATUS IN TERMS OF TONNAGE BAND.

4. Results

For each of the 10 alternative plasticisers, a full data set with identification of the substance, the physical-chemical characteristics and the toxicological and ecotoxicological data is included in Annex 4. In this, the proposed classification by the registrant is included for each endpoint. Summary tables with the main toxicological and ecotoxicological conclusions are included in Annex 2 and Annex 3, respectively.

Based on the full data sets in Annex 4, conclusions on the most important endpoints have been drawn and are summarised in Table 2 below describing the key toxicological and ecotoxicological properties (the lowest NOAEL and critical effect is indicated). Also, an evaluation of the available data sets in terms of quality and completeness is included in Table 2. For comparison, a similar evaluation of DEHP is included in Table 2. The data set for DEHP has been extracted from the RAC Background document to the Opinion on the Annex XV dossier proposing restrictions on four phthalates, 2012[14] and the SVHC support document on DEHP from ECHA, 2008[15]

Data for the 10 alternatives have been extracted from the latest REACH registration dossiers (2013) on the ECHA homepage[16], which should be the latest and most updated data sets for these substances. Furthermore, supplementary data have been received from a number of producers of the alternative plasticisers and used accordingly. For each endpoint, key studies and supplementary studies (if evaluated to be needed in the overall conclusion) from the registration are described. Only studies with Klimisch scores of 1 and 2 have been included. The Klimisch score evaluates the inherent quality of a test report or publication in relation to standardised internationally recognised test guidelines and methodology. The following Klimisch scoring system is recognised: 1 = reliable without restrictions; 2 = reliable with restriction; 3 = not reliable and 4 = not assignable.

For each study, information on test method and guideline used, including information on test species, conditions, results, and references, has been included in the evaluation. In the registration dossiers, some endpoints have been covered using weight of evidence (WOE) or read-across to similar substances. In these instances, this has been noted in the evaluation.

For the toxicological evaluation, the endpoints included in the evaluation are: Acute toxicity (LD50/LC50), irritation and sensitisation, genotoxicity/mutagenicity, carcinogenicity, repeated dose toxicity (subchronic and chronic - NOAEL/LOAEL), reproductive/developmental (NOAEL/LOAEL), toxicokinetics, and data on possible endocrine disrupting effect (if available). For the endocrine endpoint, focus will be on data from studies investigating anogenital distance and nipple retention, i.e. an antiandrogen effect, results from the Uterotrophic assay indicative of an oestrogen activity and further hormonal data (TSH, T3, T4), gene expression analysis representing major pathways of male reproduction tract development, and data on the thyroid. Furthermore, the derived no effect levels (DNEL) of the registrant are also included.

For the ecotoxicological evaluation, focus has been on CLP, PBT assessment, environmental fate and pathways, and ecotoxicological information. The endpoints included in the evaluation are: stability, biodegradation, bioaccumulation (logKOW, BCF), adsorption/desorption, aquatic and terrestrial ecotoxicity (acute (EC/LC50) and chronic data (EC/LC10 and NOEC)), and data on possible endocrine disrupting effect (if available). The derived predicted no effect concentration (PNEC) is also included.

[14] RAC Background document to the Opinion on the Annex XV dossier proposing restrictions on four phthalates, 2012.
[15] SVNC support document for the identification of DEHP as a substance of very high concern, ECHA 2008.
[16] http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

It has to be emphasised that all conclusions drawn in the registration dossiers are the responsibility of the registrants, and the results and conclusions drawn from these have therefore only been referenced in this evaluation. Thus, this evaluation should be seen as a screening of the available data rather than an in-depth evaluation.

Data on cytotoxicity, hemocompability and intracutane reactivity (if available) have been retrieved from the producers of the alternatives. Supplementary information from national and international organisations in terms of key values has been included, these data has been retrieved from a secondary source[17].

[17] Analysis of Alternatives (non-confidential report), Hazard and risk evaluation of DEHP alternatives prepared on behalf of the DEHP authorization task force (ATF), June 2013 – ARKEMA, France

Substance	CAS No	Acute (A) Local (L) sens. (S)	Carcinogenicity (C)	Mutagenic (M)	Repro toxicity (R)	Sub-/chronic toxicity	Endocrine activity	Lowest NOAEL* (critical endpoint)	DNELs (general population)	PBT/vPBT assessment
DEHP	117-81-7	+++/0 (A) +++/0 (L) +++/0 (S)	+++/+	+++/0	+++/+++	+++/+++	+++/+++	NOAEL 4.8 mg/kg bw/day (Reproduction)	0.048 mg/kg bw/day	++/0
ASE	91082-17-6	+++/0 (A) +++/0 (L) +++/0 (S)	0/NC	+/0	++/++	++/+	0/NC	NOAEL 68 mg/kg bw/day (Foetoxicity)	0.47 mg/kg bw/day	++/0
ATBC	77-90-7	+++/0 (A) +++/+ (L) +++/0 (S)	+++/0	+++/0	++/++	+++/+	0/NC	NOAEL 300 mg/kg bw/day (Liver weight)	1 mg/kg bw/day	++/0
BTHC	82469-79-2	+++/0 (A) +++/+ (L) +++/0 (S)	0/WE	++/0	++/0	+++/	0/NC	NOAEL 250 mg/kg bw/day (Liver weight, enzyme activity)	1 mg/kg bw/day	++/0
COMGHA	736150-63-3	+++/0 (A) +++/+ (L) +++/0 (S)	0/0 (WE)	+++/0	+++/0	+++/0	++/0	NOAEL > 1000 (mg/kg bw/day)	-	+++/0
DEHT	6422-86-2	+++/0 (A) +++/+ (L) +++/0 (S)	+++/0	+/0	+++/+	+++/+	++/0	NOAEL 79-102 mg/kg bw/day (Body weight, haematological effects)	3.95 mg/kg bw/day	+++/0
ESBO	8013-07-08	+++/0 (A) +++/+ (L) +++/0 (S)	+++/0	+/0	++/0	+++/+	0/NC	NOAEL 100 mg/kg bw/day (Liver weight)	0.8 mg/kg bw/day	++/0
DINA	33703-08-1	+++/0 (A) +++/0 (L) +++/0 (S)	+++/0	(+++/0) (RA)	(++/++) (RA)	(++/+) (RA)	0/NC	NOAEL 28 mg/kg bw/day (foetoxicity)	1.7 mg/kg bw/day	++/0
DINCH	166412-78-8	+++/0 (A) +++/+ (L) +++/0 (S)	+++/+	+++/0	+++/0	+++/++	++/+	NOAEL 40 mg/kg bw/day (Liver/Kidney weight)	2 mg/kg bw/day	+++/0

Substance	CAS No	Acute (A) Local (L) sens. (S)	Carcinogenicity (C)	Mutagenic (M)	Repro toxicity (R)	Sub-/chronic toxicity	Endocrine activity	Lowest NOAEL* (critical endpoint)	DNELs (general population)	PBT/vPBT assessment
DOA	103-23-1	+++/0 (A) +++/+ (L) +++/0 (S)	+++/+	+++/0	++/++	+++/0	++/+	NOAEL 28 mg/kg bw/day (foetoxicity)	1.3 mg/kg bw/day	++/0
TOTM	3319-31-1	+++/0 (A) +++/+ (L) +++/0 (S)	0/WE	+/0	++/+	++/++	++/+	NOAEL 100 mg/kg bw/day (Reproduction)	1.13 mg/kg bw/day	++/0

TABLE 2
OVERVIEW OF MAIN TOXICOLOGICAL AND ECOTOXICOLOGICAL PROPERTIES FOR THE 11 ALTERNATIVE SUBSTANCES EVALUATED TO BE POSSIBLE ALTERNATIVES TO DEHP IN MEDICAL DEVICES. DEHP IS INCLUDED FOR COMPARISON.

NOTES TO TABLE: THE INHERENT PROPERTIES FOR THE INVESTIGATED SUBSTANCES ARE SUMMARISED USING KEY PARAMETERS: ACUTE AND LOCAL EFFECTS, SENSITISATION, CARCINOGENICITY(C), MUTAGENIC TOXICITY (M), REPRODUCTIVE TOXICITY (R), ENDOCRINE ACTIVITY, PBT/VPBT ASSESSMENT. THE FOLLOWING SYMBOLS ARE USED:
/ = DATA AVAILABILITY/EFFECT WITH THE FOLLOWING SCORE SYSTEM:
0 = NO DATA/NO EFFECT
+ = ONLY IN VITRO STUDIES/SLIGHT EFFECT
++ = IN VITRO AND-OR SOME IN VIVO STUDIES/MODERAT EFFECT (NO CLASSIFICATION)
+++ = SUFFICIENT DATA SET/CLEAR EFFECT (CLASSIFICATION)
NC = NO CONCLUSION
WE = WEIGHT OF EVIDENCE
RA = READ-ACROSS
* = INDICATION WHETHER THE CRITICAL EFFECT AT HIGHER LEVEL IS IN RELATION TO FOETOXICITY/REPRODUCTION. WHEN NOT INDICATED AS FOETOXICITY/REPRODUCTIVE EFFECTS, EFFECTS ARE IN RELATION TO NON-REPRODUCTIVE EFFECTS IN ADULT ANIMALS.
( ) = INDICATES THAT THE VALIDITY OF READ-ACROSS APPROACH HAS NOT BEEN EVALUATED
- = NO CRITICAL EFFECT IDENTIFIED

5. Discussion

Publicly available data on the toxicity and ecotoxicity of 10 alternative plasticisers were extracted/compiled from the latest REACH registration dossiers (2013) on the ECHA homepage. For each of the (eco)toxicity endpoints, only the studies identified by the registrant as key studies and supplementary studies were included, and also the studies with Klimisch scores of 1 and 2 were included. The Klimisch scores of 1 and 2 indicate that the data were of good quality, usually test data from studies performed in accordance with internationally recognised test guidelines (or similar to) and GLP regulations.

REACH registration dossiers were available for most of the alternative substances. However, for BTHC (CAS 82469-79-2) data were limited, and for DINA (CAS 33703-08-1) read-across was used for most endpoints. In terms of DINCH, the key studies in the registration dossier are presented with rather few details, and supporting information has therefore been retrieved from other sources (NICNAS, GreenScreen Assessment from Toxservices).

5.1 Toxicological properties of the alternatives

In general, low acute toxicity was observed for the 10 alternative plasticisers. Furthermore, the alternatives were evaluated not to have potential for skin and eye irritation or skin sensitisation; hence none of the alternatives are classified for these effects. This is very comparable to the toxicological profile for the phthalates for these endpoints.

With respect to repeated dose toxicity, the relatively high NOAEL values indicate no need for classification (STOT RE) as also concluded by the registrants. None of the four phthalates (DEHP, BBP, DBP and DIBP) are classified for STOT RE.

In terms of genotoxicity, no effects were observed *in vitro* and *in vivo*; hence no classification has been applied for any of the alternatives. Data on carcinogenicity did not indicate any concern either, and thus no substances have been classified for this endpoint. No classification for these endpoints applies for the four phthalates.

For developmental toxicity and fertility, the data do not lead to classification (Repr) for any of the alternative substances according to the registrants. This is in contrast with the four phthalates (DEHP, BBP, DBP and DIBP) classified as Repr 1B; H360FD/ H360Df.

Three of the alternatives (COMGHA, DEHT and DINCH) have been investigated for reproductive toxicity over two generations (OECD 416). For COMGHA), supplementary endpoints investigating a possible endocrine activity were included (i.e. anogenital distance and nipple retention indicative of a possible antiandrogen activity and impact on thyroid weight). Also, assessment of developmental neurotoxicity (OECD 426) was included in this study design. For DEHT and DINCH, information on whether the same type of effect parameters were included in the two-generation reproduction studies could not be retrieved; however they were investigated in developmental studies for the substances. Also investigations on thyroid weight were included in the two-generation studies.

For five of the alternatives (ASE, BTHC, DINA, DOA and ESBO), reproductive toxicity over one generation (OPECD 415) has been investigated. For ATBC, no information on reproductive toxicity could be retrieved from the registrations, and for TOTM the only identified data set from the registration dossier was from a screening study on reproduction and development (OECD 421).

In terms of data specifically examining endocrine activity, the number of investigations were limited for the alternatives; only a few have actually been investigated and with different levels of information. For COMGHA, specific investigations on anogenital distance and nipple retention have been conducted. For DEHT, data on anogenital distance, gene expression on male reproductive tract development, and data from an Uterotrophic assay are available. For DINCH, data on anogenital distance, hormonal levels of TSH, T3 and T4, thyroid weight and further investigations on peroxisome proliferation (PPARα receptor) are available.

Based on the collected information in Table 2 supplemented with the information in the data sheets (Appendix 4), the following observations for the alternatives can be made:

For **ASE**, the REACH registration dossier indicated a NOAEL of 228 mg/kg bw/day (90-day) based on growth reduction, a NOAEL of 68 mg/kg bw/day (one-generation reproduction) based on foetotoxicity, and a NOAEL of 1000 mg/kg bw/day for developmental toxicity. The data set from the registration dossier was not adequate for a high tonnage registration (Annex X: > 1000 tpa.), i.e. no two-generation reproduction toxicity study or carcinogenicity study were available. Also, no data were available for *in vivo* genotoxicity. In terms of a possible endocrine activity, no data were available in the registration dossier. Overall, important data is needed for ASE in terms of reproductive toxicity (multi-generation study) to further evaluate fertility and developmental effects, carcinogenicity and endocrine activity.
In 2009, EFSA concluded ASE to be a substance for which an ADI or a TDI could not be established, but where the present use could be accepted, and with a restriction of the content in food of 0.05 mg/kg food. Furthermore, ASE must not be used in articles for contact with fatty foods (EFSA, 2009)[18].

For **ATBC**, a NOAEL of 300 mg/kg bw/day was found for chronic toxicity, a NOEL of 1000 mg/kg bw/day for carcinogenic effects, and a NOAEL of 250 mg/kg bw/day for developmental toxicity (data from these studies were however limited). No data of a possible endocrine activity were available in the REACH registration dossier. In terms of genotoxicity, data from *in vitro* and *in vivo* studies indicate that ATBC does not have a genotoxic potential. Overall, important data are needed for ATBC in terms of reproductive toxicity and endocrine activity. Furthermore, the Cosmetic Ingredient Review Expert panel (CIREP) has evaluated ATBC and concluded its use as safe in cosmetics[19].

For **BTHC**, no registration dossier could be retrieved. Data were extracted from a previous evaluation performed by SCENIHR[20] and from a safety data sheet supplied from the producer. The key NOAEL was 250 mg/kg bw/day (28-day, oral). Furthermore, BTHC was shown not induce hepatic peroxisome proliferation (six weeks study). No effects of BHTC in terms of reproductive or developmental toxicity were found, and a NOEL of 1.2% (in diet) and 500 mg/kg bw/day for reproductive and developmental toxicity was identified, respectively (however, from studies not performed in accordance to OECD guidelines). Based on the available genotoxicity data (*in vitro* and *in vivo*), SCENIHR evaluated BTHC to be non genotoxic. Furthermore, no life-time carcinogenic study has been performed, but based on an overall weight of evidence approach (BTHC is neither genotoxic nor a peroxisome proliferating agent), the substance was considered by SCENIHR to be of no concern with respect to carcinogenicity.
Overall, important data are needed for BTHC in terms of reproductive toxicity (multi-generation study), developmental toxicity testing, and endocrine activity. Also repeated dose toxicity data (90 day/chronic toxicity studies) are needed.

For **COMGHA**, in general the NOAELs identified were > 1000 mg/kg bw/day (studies on 90-day, chronic toxicity, 2-generation reproduction, developmental toxicity and developmental neurotoxicity), and it was stated that no antiandrogenic activity could be observed. No life-time carcinogenic study has been performed, but based on weight of evidence it was concluded by the registrant that COMGHA has no carcinogenic potential. This was supported by the data from a panel of *in vivo* and *in vitro* genotoxicity studies showing no genotoxic potential. Overall, a full data set for an Annex X registration (> 1000 tpa) is available for COMGHA, including data from a combined multi-generational

[18] Scientific Opinion on the safety evaluation of the substance, alkyl(C10-C21)sulphonic acid, esters with phenol, CAS No. 91082-17-6, for use in food contact materials EFSA Panel on food contact materials, enzymes, flavourings and processing aids (CEF), The EFSA Journal, 7, 1398
[19] Final report on the safety assessment of acetyl triethyl citrate, acetyl tributyl citrate, acetyl trihexyl citrate, and acetyl trioctyl citrate International Journal of Toxicology, 21, Suppl. 2, 1-17
[20] SCENIHR opinion on the safety of medical devices containing DEHP plasticised PVC or other plasticisers on neonates and other groups possibly at risk.

reproduction toxicity and developmental neurotoxicity study with endocrine related endpoints included (anogenital distance and nipple retention). In terms of the available toxicological data, no concern is indicated. Overall, the data do not indicate a need for further investigations on endocrine activity.
Furthermore, COMGHA was evaluated by The Australian authorities (NICNAS) that concluded COMGHA to be without hazards or human health risks to workers under defined occupational settings and to the general public when used in the proposed manner (e.g. plasticiser in PVC and other plastic applications, food contact materials, toys and medical devices)[21].

For **DEHT**, the key NOAELs are 79-102 mg/kg bw/day (chronic toxicity), > 666 mg/kg bw/day (carcinogenicity), 277 mg/kg bw/day (90-day), 447-747 mg/kg bw/day (reproductive and development toxicity). A number of *in vitro* genotoxicity studies did not indicate a genotoxic potential. No *in vivo* genotoxicity studies were available in the registration dossier. DEHT is a phthalate and is not considered to be a part of the common phthalate ester class, as it is not *ortho*-substituted. In terms of a possible endocrine activity, the available data from the REACH registration indicated no antiandrogenic effect as sexual differentiation, and development was unaffected in male offspring. This conclusion was supported by supplementary data from a negative Uterotropic assay and gene expression assays investigating gene pathways for normal male reproductive tract development. Overall, a full data set for an Annex X registration (> 1000 tpa.) is available for DEHT. In terms of the available toxicological data, no concern is indicated, and no further data are needed.
This was also concluded by a hazard assessment performed by GreenScreen Assessment from Toxservices[22]. A low concern for developmental and reproductive toxicity was concluded in the assessment. Furthermore, it was concluded in the assessment that DEHT is unlikely to affect the endocrine activity in male rats based on the results from the 2-generation reproduction study and developmental studies (spermatogenic assessment, reproductive organ weights, anogenital distance, and nipple retention). From the results of the Uterotrophic assay and the developmental studies, it was concluded that DEHT is unlikely to affect endocrine activity in female rats. It was however noted in the assessment that limited data were available to assess potential thyroid effects.

For **ESBO**, the key NOAELs are 100 mg/kg bw/day (systemic toxicity from screening study), 1000 mg/kg bw/day (reproductive and developmental toxicity) and 1000 mg/kg bw/day (carcinogenicity). No data for endocrine activity. No genotoxicity was observed from a number of *in vitro* genotoxicity studies, no data on *in vivo* genotoxicity were available in the REACH registration dossier.
Overall, further data is needed from a multi-generation reproduction study, e.g. 2-generation reproduction (OECD 416) or the extended 1-generation reproduction (OECD 443) supplemented with endocrine related endpoints. Based on the available data, the critical effect of ESBO is liver toxicity.

For **DINA**, the REACH registration dossier consisted of a combination of test data for DINA and test data for a structurally similar substance - bis(2-ethylhexyl) adipate) (CAS no 103-23-1). The use and relevance of this read-across approach has not been evaluated in this report. The key NOAELs identified are 200-595 mg/kg bw/day (28 and 90-day studies), 28-170 mg/kg bw/day (reproductive and developmental toxicity studies) and 600 mg/kg bw/day (carcinogenicity). Carcinogenicity was however observed > 1000 mg/kg bw/day, and developmental toxicity (reduced ossification, increase in visceral variants) was observed at 170 mg/kg bw/day.
These data are all based on read-across to bis(2-ethylhexyl) adipate) (CAS no 103-23-1) identified as a similar substance. No information was included in registration on possible endocrine activity. Furthermore, a full data set for genotoxicity (*in vitro/in vivo*) did not indicate a genotoxic potential using the data for the structural similar substance. Overall, important data are needed for DINA (or the structural similar substance) in terms of reproductive toxicity (multi-generation study, e.g. 2-generation reproduction (OECD 416) or the extended 1-generation reproduction (OECD 443)) and endocrine activity.

For **DINCH**, the key NOAELs are 40 mg/kg bw/day (chronic toxicity), 107 mg/kg bw/day (90-day) and 1000- 1200 mg/kg bw/day (reproductive and developmental toxicity). A full data set for genotoxicity (*in vitro/in vivo*) indicated no

[21] NICNAS, Full public report, Glycerides, castor-oil mono-, hydrogenated, acetates, Glycerides, castor-oil mono-, hydrogenated, acetates, 2009
[22] GreenScreen™ Assessment for Di(2-ethylhexyl) terephthalate (DEHT) (CAS #6422-86-2) October 11th, 2012.

concern. In terms of a carcinogenic potential, data were included in the REACH registration dossier, but information were limited. NOAELs for carcinogenicity were ≥ 200 mg/kg bw/day (male) and 1000 mg/kg bw/day (female) based on dose-related follicular cell hyperplasia and increased number of follicular adenomas in the thyroid gland at higher dose levels. A NOAEL of 40 mg/kg bw/day was identified for chronic toxicity based on liver and kidney weight changes observed at higher dose levels.
A detailed data set was not available in the REACH registration dossier, including data on endocrine activity. Evaluations performed by NICNAS and GreenScreen Assessment from Toxservices were therefore consulted.
NICNAS concluded in their assessment of DINCH[23] that based on the data from the reproductive toxicity and developmental studies, there were no antiandrogenic effects (no significant treatment – related effects on anogenital distance in any of the reproductive toxicity studies). In general, no substance related adverse effects on normal sexual development and differentiation. Furthermore, NICNAS stated that the observed thyroid effects in rats (90-day and chronic) were evaluated to be associated with an indirect mechanism based on results from mechanistic studies, and further that DINCH was evaluated not to be a peroxisome proliferator
A new evaluation of DINCH, i.e. the GreenScreen Assessment from Toxservices [24], is in contradiction with the former conclusions, concluding that DINCH has moderate endocrine activity. This evaluation has however been questioned by BASF[25] claiming that the conclusions by Toxservices for potential endocrine activity are incorrect and inconsistent with those reached by BASF, the European Food Safety Authority (EFSA), the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS), and the EU Scientific Committee on Emerging and Newly-identified Health Risks (SCENIHR).
Overall, a full data set for an Annex X registration (> 1000 tpa) is available for DINCH, including some data on a possible endocrine disrupting effect. Further data are needed to fully explore this potential.

For **DOA**, the key NOAELs are 28-170 mg/kg bw/day (developmental/foetotoxicity), 170 mg/kg bw/day (reproduction), 600 mg/kg bw/day (chronic toxicity). No carcinogenicity was observed, NOAEL was 1250 mg/kg bw/day. In terms of a possible endocrine activity, no specific data on this endpoint were included in the REACH registration dossier. In relation to a possible endocrine activity, the following is referenced from secondary source [26]: "some studies reported the lack of an antiandrogenic effect or estrogenic activity. No estrogenic activity was observed in transgenic mice, expressing an oestrogen receptor (ER) - mediated luciferase (luc) reporter gene system. DEHA affected thyroid hormone function in rats (TH-dependent rat pituitary GH3 cell proliferation, T-screen), but not the oestrogen receptor function in human breast MVLN cells". According to the same reference, no effects were noted in a developmental toxicity test using dose levels of up to 800 mg/kg bw/day with respect to reproductive hormones, sperm quality, weight and histopathology of male reproductive organs. It should be noted that DOA has been included in the CoRAP[27] list due to human health concerns in terms of reproduction[28]. In the background document for the inclusion to this list, it is stated that DOA is suspected to have effects on the male reproductive system based on the structural similarities and metabolism with DEHP. Furthermore, in a number of reproductive toxicity studies, DOA did produce effects on development and reproduction.
Overall, the critical effects of DOA are foetotoxicity (reduced ossification and increased incidence of visceral variants) identified from the registration dossier. Further data are needed from a multi-generation reproduction study, e.g. 2-generation reproduction (OECD 416) or the extended 1-generation reproduction (OECD 443) supplemented with endocrine related endpoints.

For **TOTM**, the key NOAELs were 225 mg/kg bw/day (90-day), 1oo mg/kg bw/day (screening study of reproduction screening study – OECD 421) as effects on spermatogenesis were seen at 300 mg/kg bw/day and 1050-500 mg/kg bw/day (developmental toxicity) for maternal and developmental toxicity, respectively. No carcinogenic test data were available, but a QSAR prediction showed TOTM not to have alert for carcinogenicity. A panel of *in vitro* genotoxicity tests

[23] NICNAS Full public report 1,2-Cyclohexanedicarboxylic acid, 1,2-diisononyl ester ('Hexamoll DINCH'); File No: EX/170 (STD/1259) February 2012.
[24] GreenScreen™ Assessment for Hexamoll® DINCH® (Diisononyl cyclohexanedicarboxylate) (CAS #166412-78-8, 474919-59-0) May 1, 2013.
[25] Comments on final GreenScreen™ assessment of Hexamoll® DINCH®, BASF Corporation, May 30, 2013
[26] Analysis of Alternatives (non-confidential report), Hazard and risk evaluation of DEHP alternatives prepared on behalf of the DEHP authorization task force (ATF), June 2013 – ARKEMA, France
[27] Community Rolling Action Plan
[28] Justification for the selection of a candidate CoRAP substance http://echa.europa.eu/documents/10162/2bc79569-1f0d-4c35-ad6e-29c4c7656298

did not indicate a genotoxic potential. In repeated dose toxicity studies, TOTM was found to induce liver enlargement, increases in palmitoyl-CoA oxidation and in the activities of catalase and carnitine acetyl transferase and induction of slight peroxisome proliferation. This is the same spectrum of morphological and biochemical changes to the rat liver as DEHP although TOTM was much less potent. TOTM was found to be a peroxisome proliferator; a mechanism considered not likely relevant to humans.
Overall, in terms of fertility and development, a reduced number of spermatocytes and spermatids were seen in the screening study (OECD 421), but in a supporting mechanistic transcriptional profiling study no significant repressive effect on the expression of genes in pathways known to be involved in steroidogenesis and testes development were seen in contrast to substances having positive responses in the study (MEHP and DEHP). Furthermore, in a developmental toxicity study (OECD 414) no effects on sexual maturation or development of the reproductive tract in male or female offspring were attributed to treatment. Observations on male offspring in terms of retained areolar region and slightly higher increase in displaced testes were stated to be transient and within the range of historical control data, respectively. In the above mentioned 90-day oral toxicity study, no adverse effects were observed on the spermatogenic cycling (histology and staging of testis), the oestrous cycle and on the histology of the reproductive organs. However, the studies described above were not performed using the same strains of rats.

A recent evaluation by GreenScreen Assessment from Toxservices[29] indicated a moderate concern for reproductive toxicity. In this assessment, TOTM was classified as a GHS Category 2 reproductive toxicant based on absence of statistical evaluation and further historical data in the OECD 421 study, and a general lack of reproductive toxicity studies.

Overall, further data is needed from a multi-generation reproduction study e.g. 2-generation reproduction (OECD 416) or the extended 1-generation reproduction (OECD 443) supplemented with endocrine related endpoints. Although conflicting data (as indicated above) the NOAEL of 100 mg/kg bw/day found in the reproductive toxicity screening study is at present considered the most conservative NOAEL for reproductive toxicity.

5.2 Ecotoxicological properties of the alternatives

Environmental profiles for the 10 alternatives have been established. These are reported in separate datasheets (Annex 4) and summary table (Annex 3). The environmental profiles can be divided into environmental fate properties and hazard profile properties:

- Overall, the alternatives have very similar fate profile as the phthalates; each of them has low water solubility and a high octanol-water partition coefficient.

- In general and as for the phthalates, the alternatives with a log Kow value below approx. 10 are readily biodegradable and alternatives with log Kow values above 10 are inherently biodegradable.

- Overall and similar to the phthalates, none of the alternatives tends to concentrate in water and air, but into sediment and soil.

- None of the alternatives is assessed as being PBT or vPvB substances. It is however noted that TOTM (CAS No 3319-31-1) has been listed on the CORAP list for environmental concerns/suspicion of PBT properties. Information supplied by the producer[30] however states that the suspected PBT properties of TOTM have now been rejected, based on an evaluation performed by Competent Authority, concluding that there is no concern regarding the PBT toxicity criterion. It is further stated by the producer that supplementary studies are planned to further explore this property.

[29] GreenScreen™ Assessment for Tris(2-ethylhexyl) trimellitate (TEHTM) (CAS #3319-31-1) May 21 2013
[30] Statement – Update on TOTM Substance Evaluation, Oxea Gmbh, Germany, 2013

- Only one of the alternatives, ATBC, was screened to be bioavailable (based on QSAR prediction). A predicted non-bioavailability (QSAR) indicates a low potential for being biologically active (e.g. a low potential to have endocrine disrupting properties). No ecotoxicological data were found, which could either support or reject the hypothesis that ATBC may cause endocrine disrupting effects. QSAR prediction of bioavailability was not calculated for COMGHA, but toxicological data show that COMGHA causes no antiandrogen effects.

- There is a general problem with the reported ecotoxicity data, as the reported ecotoxicological effect concentrations for the alternatives (as for the phthalates) are reported as "larger than" or often do exceed the water solubility of the tested substance. This means that the determined toxicities are not necessarily caused by the dissolved substances, but can be a consequence of physical effects. This indicates that the alternatives do not have any acute ecotoxicological effects on algae, crustaceans and fish.

- Very few ecotoxicological data for sediment and soil dwelling organism are found.

- The PNEC values for soil and sediment for DEHP are generally higher than the reported PNEC-values for the alternatives, indicating a lower toxicity of DEHP compared to the alternatives. However, this may be a result of the fact that a better data set exists for DEHP compared to the alternatives.

Similar to DEHP, the substances COMGHA, DEHT, DINA and DOA are reported as being readily biodegradable. No indications of endocrine disrupting effects in the environment for these substances have been found.

None of the alternatives is assessed as being PBT or vPvB substances. It is however noted that TOTM (CAS No 3319-31-1) has been listed on the CORAP list for environmental concerns/suspicion of PBT properties. Information from the producer however rejects this concern based on feedback from competent authority, and further studies are planned to explore this. In conclusion, considering the similar environmental effects profiles to DEHP, the evaluated alternative plasticisers may be substitutes for DEHP based on environmental hazard profiles.

In the REACH registrations, the alternatives are registered in relation to opened/closed industrial end uses and wide dispersive uses, and therefore, significant releases into the environment are expected. Overall, none of the alternatives tends to concentrate in water, but into sediment and soil. In terms of a possible hormone-like effect, data are available for a few of the alternatives, but conclusive data are lacking and more data are needed to fully explore this potential.

6. Conclusion

Evaluations of the 10 alternative plasticisers have been based on the study summaries and conclusions drawn in the registration dossiers by the registrants supplemented with recent evaluations from regulatory bodies, evaluations performed by contract and secondary literature, i.e. NICNAS and GreenScreen Assessment from Toxservices. It must be emphasised that all conclusions drawn in the registration dossiers are the responsibility of the registrants, and the results and conclusions drawn from these have therefore only been referenced in this evaluation. Thus, this evaluation should be seen as a screening of the available data rather than an in-depth evaluation.

In terms of the human health hazard profiles, it can be noted that the DNELs (general population) derived by the registrants for the alternative plasticisers are all higher in comparison with the DNELs (general population) for DEHP. Furthermore, it is noted that the alternatives did not have the same type of toxicological profile as seen for DEHP in terms of reproduction and development. The exception is DOA which is suspected to have effects on the male reproductive system based on the structural similarities and metabolism with DEHP.

For the carcinogenic endpoint, a data set from a two-year study (OECD 452) was available for ATBC, DEHT, ESBO, DINA, DINCH and DOA. For BTHC and COMGHA, a weight of evidence approach was applied using available data from genotoxicity studies and repeated toxicity studies. For TOTM, a weight of evidence approach was applied using QSAR analysis. No information was available for ASE.

In terms of repeated dose toxicity studies, for ATBC, DEHT, DINCH, DOA and ESBO a data set from combined chronic toxicity and carcinogenicity (OECD 453) was available. For COMGHA, a data set from a chronic toxicity study was available (OECD 452). For ASE, DINA and TOTM, a data set from a 90-day toxicity study (OECD 408) study was available. A data set from a 28-day toxicity study (no guideline) was available for BTHC.

For the alternatives COMGHA, DEHT and DINCH, a data set fulfilling the requirements for a high tonnage registration (Annex X) in relation to reproduction and development was available, i.e. a reproductive toxicity study over two generations (OECD 416). For five of the alternatives (ASE, BTHC, DINA, DOA and ESBO), reproductive toxicity over one generation (OPECD 415) has been investigated. For ATBC, no information on reproductive toxicity could be retrieved from the registration, and for TOTM, the only identified data set from the registration dossier was from a reproduction and developmental toxicity screening study (OECD 421). For TOTM, supplementary information on reproduction was available from a 90-day toxicity study and from a mechanistic transcriptional profiling study.

In relation to the potential of specific endocrine activity of the alternatives, more data are needed to fully explore these properties. Only data on COMGHA, DEHT, DINCH, DOA and TOTM were available with varying levels of information and type of endpoints investigated. For these, a clear and definite conclusion on a possible endocrine disrupting effect was not possible, as the underlying mechanism of all types of endocrine disrupting effects has not been fully investigated. It is however noted that the available data for COMGHA and DEHT do not indicate a course of concern.

A discussion is ongoing in relation to DINCH due to potentially relevant effects in reproductive/developmental and thyroid endpoints. It is noted that this has been argued from the producer not to be relevant effects and further supported by authorities (NICNAS, EFSA and SCENIHR). DOA (CAS No 103-23-1) raises some concern for reproductive toxicity and developmental toxicity (foetotoxicity i.e. reduced ossification and increased incidences of visceral variations)

and it has recently been listed on the CORAP list[31] due to human health consideration based on the structural similarities and metabolism with DEHP. Furthermore, DOA shows some indications of endocrine activity, i.e. affected thyroid hormone function[32].

In terms of potential exposure from the alternative substances, more data would be needed to assess the migration behaviour of the alternative substances, and more data is needed to fully explore these properties. Until then and considering their similar physical-chemical properties, similar migration behaviour as for the phthalates may be a starting assumption for consumer exposure from articles, as migration of plasticisers from articles is considered to be the most relevant exposure situation for consumers. It is though noted that TOTM seem to have a very low migration rate in PVC based on information received from the producer.

In conclusion, 10 alternatives to DEHP have been evaluated in terms of their human health hazard profiles based on the available data sets. For most substances, there is not sufficient information regarding reproductive toxicity and potential for endocrine disrupting effects in order to make firm conclusion on these endpoints. Although not tested to the same degree as e.g. DEHP (with respect to reproductive toxicity and endocrine disruption), the substances COMGHA, DEHT, and DINCH may be seen as the most promising alternatives, as these substances have extended data sets (complying to Annex X data requirements, i.e. a two-generation reproduction study) and without indicating specific concern for reproductive toxicity or endocrine activity. It has to be emphasised that this evaluation is primarily based on the available data as presented by the registrants in the REACH registration dossiers of the substances.

In terms of the environmental hazard profiles, it seems that the alternative plasticisers show similarities to DEHP. COMGHA, DEHT, DINA, and DOA are assessed to be readily biodegradable, whereas ASE, ATBC, DINCH, and TOTM are assessed to be inherently biodegradable. It is noted that TOTM (CAS No 3319-31-1) has been listed on the CORAP list for environmental concerns/suspicion of PBT properties, but information from the producer however rejects this concern based on the feedback from competent authority. The producer has indicated that further studies are ongoing to explore this property.

The alternatives appear not to have any acute ecotoxicological effects on algae, crustaceans and fish.
Only one of the alternatives, ATBC, was screened to be bioavailable (based on QSAR prediction) indicating a potential for being biological active. No toxicological data were found which either could support or reject the hypothesis that ATBC may cause endocrine disrupting effects. QSAR prediction of bioavailability was not performed for COMGHA, but toxicological data show that COMGHA causes no antiandrogenic effects.

In conclusion, considering the similar environmental effects profiles to DEHP, the evaluated alternative plasticisers may be used as substitutes for DEHP based on environmental hazard profile.

[31] Justification for the selection of a candidate CoRAP substance http://echa.europa.eu/documents/10162/2bc79569-1f0d-4c35-ad6e-29c4c7656298

[32] Analysis of Alternatives (non-confidential report), Hazard and risk evaluation of DEHP alternatives prepared on behalf of the DEHP authorization task force (ATF), June 2013 – ARKEMA, France

Appendix 1: Producers and trade names/synonyms of the 10 alternative plasticisers

Substance	Group of plasticiser	CAS no	Producer	Trade name / synonyms
ASE	Sulphonates	91082-17-6	LanXess (EU) Other?	Mesamoll II
ATBC	Citrates	77-90-7	Vertellus, (US) Jungbunzlauer (EU) Provion (EU) Etc.	Citroflex A-4 Citrofol BII Proviplast 2624
BTHC	Citrates	82469-79-2	Vertellus (US)	Citroflex B-6
COMGHA	Castor oil Derivatives	736150-63-3	DuPont (EU)	Soft-n-Safe
DEHT	Terephthalate	6422-86-2	Eastman (US) Ineos (EU) Oxea (EU) Provion (EU) ZAK (EU) LGChem (Asia) Plastay (Asia) Ela (Asia) Advansa (Asia) Etc.	Eastman 168 Cereplast 100S Oxsoft GPO Proviplast 2388 Oxoplast OT LGflex GL300 Sunfleks Elafleks Sasa Plus 88
DINA	Aliphatic dibasic esters	33703-08-1	Exxon Mobil (US) BASF (EU) LanXess (EU) Etc.	Jay flex-DINA Plastomoll DNA Adimoll DN
DINCH	Cyclohexanes	166412-78-8	BASF Evonik Other?	Hexamoll DINCH Elatur CH
DOA	Adipates	103-23-1	Eastman BASF Ela Oxea Plastay Elekeiroz Etc.	Eastman DOA Plastomoll DOA DOA Dioctyl Adipate Oxsoft DOA D.O.A. DOA
ESBO	Epoxy esters And epoxidized Oils	8013-07-8	Galata Akcros Plastay Emery Oleochemicals Etc.	Drapex 39 Lankroflex E2307 E.S.B.O. Edenol D81
TOTM/TEHTM	Trimellates	3319-31-1	Oxea Eastman BASF Elekeiroz Polynt Etc.	Oxsoft TOTM Eastman TOTM Palatinol TOTM TOTM Diplast TM

TABLE 3
THE TABLE REPRESENTS AN OVERVIEW OF PRODUCERS AND TRADE NAMES/SYNONYMS OF THE 10 ALTERNATIVE PLASTICISERS. THE TABLE HAS BEEN ESTABLISHED BASED ON FEEBACK FROM THE PRODUCERS OF THE ALTERNATIVES AND FROM MANUFACUTURER OF MEDICAL DEVICES

Appendix 2: Main toxicological properties of the 10 alternative plasticisers

Substance	CAS No	Acute toxicity (LD50) Oral/dermal/ Inhalation (mg/kg bw) (mg/L air)	Irritation/ Sensitisation	Subchronic/ Chronic (mg/kg bw/day) (mg/L air)	Carcinogenicity (mg/kg bw/day)	Mutageni-city / Genotoxicity	Reproductive toxicity (mg/kg bw/day)	Developmental toxicity (mg/kg bw/day)	Other data
DEHP	117-81-7	>10000/- /10	Irr. D (-) Irr. E (-)/ Sens. (-)	NOAEL 14	NOAEL 29-98	In vitro (-) In vivo (-/+)	NOAEL 20	NOAEL 4.8	Clear endocrine activity
ASE	91082-17-6	>15000/>1055/-	Irr. D (-) Irr. E (-)/ Sens. (-)	NOAEL (90d) 228-283	ND	In vitro (-) In vivo (ND)	NOAEL 68 (GE) NOAEL 68 (DE)	NOAEL (MA) 300 NOAEL (DE) 1000	C (ND) H(ND) IC (ND)
ATBC	77-90-7	31500/>1000/-	Irr. D (-)/ Irr. E (+/-)/ Sens. D (-)	NOAEL (90d) 1000 NOAEL (CH) 300 (M)	NOEL 1000 NOEL 1000	In vitro (-) In vivo (-)	WOE	NOEL (MA 50 NOEL (DE) 250	C (ND) H(ND) IC (ND)
BTHC	82469-79-2	5000/- /-	Irr. D (+/-)/ Irr. E (+/-)/ Sens. D (-)	NOAEL (28d) 250	ND (WOE)	In vitro (-) In vivo (-)	NOAEL 1.2% (GE) NOAEL 1.2% (DE)	NOAEL 500 (DE)	C (ND) H(ND) IC (ND)
COMGHA	736150-63-3	>2000/>2000/-	Irr. D (-) Irr. E (-)/ Sens. (-)	NOAEL (90d) 5000 NOEAL (CH) 1333	ND (WOE)	In vitro (-) In vivo (-)	NOAEL (FE) ≥1159 NOAEL (DE)≥1159 NOAEL (GE)≥1159	NOEL (MA 1000 NOEL (DE) 1000	C (-) H(-) IC (ND)
DEHT	6422-86-2	5000/20000/-	Irr. D (-) Irr. E (+/-) Sens. (-)	NOAEL (90d) 277 (M) NOAEL (CH) 79-102 NOAEL (14d) 0.072 (M)	NOAEL 666 (M) NOAEL 901 (F)	In vitro (-) In vivo (ND)	NOAEL (FE) 447-1349 NOAEL (DE) 133-516 NOAEL (GE) 133-516	NOAEL 458 (MA) NOAEL 747 (DE)	C (ND) H(ND) IC (ND
DINA	33703-08-1	5000/-/5.7	Irr. D (-) Irr. E (-)/ Sens. (-)	NOAEL (28d) 200 NOAEL (90) 200	NOAEL 600	In vitro (-) In vivo (-)	NOAEL (FE) 170 NOAEL (DE) 170 NOAEL (GE) 170	NOAEL 1000 (MA) NOEL 28 (DE)	C (ND) H(ND) IC (ND

Substance	CAS No	Acute toxicity (LD50) Oral/dermal/ Inhalation (mg/kg bw) (mg/L air)	Irritation/ Sensitisation	Subchronic/ Chronic (mg/kg bw/day) (mg/L air)	Carcinogenicity (mg/kg bw/day)	Mutageni-city / Genotoxicity	Reproductive toxicity (mg/kg bw/day)	Developmental toxicity (mg/kg bw/day)	Other data
DINCH	166412-78-8	5000/2000/-	Irr. D (-) Irr. E (-)/ Sens. (-)	NOAEL (28d) 318 (M) NOAEL (90d) 107 (M) NOAEL (CH) 40 (M)	NOAEL 40 (M) NOAEL 200 (F)	In vitro (-) In vivo (-)	NOAEL (FE) 1000 NOAEL (DE) 1000 NOAEL (GE) 100	NOAEL 1000 (MA) NOEL 1000 (DE)	
DOA	103-23-1	25/-/>5.7	Irr. D (-) Irr. E (-) Sens. (-)	NOAEL(28d) 200 NOAEL (CH) 600	NOAEL 600	In vitro (-) In vivo (-)	NOAEL (FE) 1080 NOAEL (DE) 170 NOAEL (GE) 170	NOEL (m) 170 NOEL (f) 28	C (ND) H(ND) IC (ND)
ESBO	8013-07-8								
TOTM/TEHTM	3319-31-1	2000/2/2600	Irr. D (-) Irr. E (-)/ Sens. (-)	NOAEL(90d) 225	-	In vitro (-) In vivo (-)	NOAEL (FE) 100 (M) NOAEL (DE) 1000 NOAEL (GE) 1000	NOEL (MA) 1050 NOEL (DE) 1050	C (ND) H(ND) IC (ND

TABLE 4
OVERVIEW OF THE MAIN TOXICOLOGICAL PROPERTIES OF THE 10 ALTERNATIVE PLASTICISERS EVALUATED TO BE POSSIBLE ALTERNATIVES TO DEHP IN MEDICAL DEVICES. DEHP IS INCLUDED FOR COMPARISON.

NOTES TO TABLE: THE INHERENT PROPERTIES OF THE 10 ALTERNATIVE PLASTICISERS ARE SUMMARISED FOR KEY PARAMETERS: ACUTE AND LOCAL EFFECTS, SENSITISATION, CARCINOGENICITY (C), MUTAGENIC TOXICITY (M), REPRODUCTIVE TOXICITY (R), SUBCHRONIC/CHRONIC TOXICITY, DEVELOPMENTAL TOXICITY AND OTHER DATA (C=CYTOTOXICITY, H=HEMOCOMPABILITY, IC=INTRACUNA REACTIVITY). MA=MATERNAL TOXICITY, DE=DEVELOPMENTAL TOXICITY, FE=FERTILITY. GE=GENERAL TOXICITY
EFFECTS LEVELS IN TERMS OF LD50/LC50 AND NOAEL VALUES ARE INCLUDED. ND=NO DATA

Appendix 3: Main ecotoxicological properties of the 10 alternative plasticisers

Substance	CAS	PBT assessment	Biodegradability	Water solubility	log K_{ow}	Vapour pressure (Pa)	K_h (Pa m^3/mol)	K_{oc}
DEHP	117-81-7	The substance is not PBT / vPvB	readily biodegradable (EU Method C.4-C Determination of the "Ready" Biodegradability - Carbon Dioxide Evolution Test)		7.66	0.0016	-	log Koc: 5.68
ASE	91082-17-6	-	C10-21-alkane, Ph esters is not readily biodegradable, but is degradable as the pass level of 60 % degradation (BOD) was achieved after 47 days (EU Method C.4-D)	2.2 mg/L	5.7 - 11.3	0.000294	0.04 - 0.061	log Koc: 4.5 - 9.3
ATBC	77-90-7	The substance is not PBT / vPvB	inherently biodegradable	4.49 mg/L	4.86	0.0494	4.434	log Koc: 4.271
BTHC	82469-79-2	-	Not meeting the conditions of ready biodegradable	0.61 mg/L	8.21	<0.000001 Pa	3.70×10^{-4}	log Koc: 7.0478
COMGHA	736150-63-3	-	readily biodegradable (OECD Guideline 301 F)	<0.33 mg/L	6.4	0.000000048	-	log Koc: 5.4
DEHT	6422-86-2	The substance is not PBT / vPvB	readily biodegradable (OECD Guideline 301 B)	ca. 0.4 µg/L	7.81	< 0.001	-	log Koc: 5.43
DINA	33703-08-1	The substance is not PBT / vPvB	readily biodegradable (OECD Guideline 301 F)	0.0032 mg/L	9.56 - 10.4	0.0000002	9.210442	log Koc: 5.291
DINCH	166412-78-8	-	inherently biodegradable (no conclusion in dossier) (-)	<0.02 mg/L	10	0.000022	7.15	log Koc: 6.59
DOA	103-23-1	The substance is not PBT / vPvB	readily biodegradable	0.0032 mg/L	8.94	0.00003	5.06	log Koc: 4.687

Substance	CAS	PBT assessment	Biodegradability	Water solubility	log K_{ow}	Vapour pressure (Pa)	K_h (Pa m^3/mol)	K_{oc}
ESBO	8013-07-08	-	-	-	-	-	-	-
TOTM/TEHTM	3319-31-1	Further information relevant for the PBT assessment is necessary	inherently biodegradable, fulfilling specific criteria	3.06 µg/L	8	ca. 0.000000068	0.0506	log Koc: 22.96

TABLE 5
OVERVIEW OF THE MAIN ECOTOXICOLOGICAL AND PHYSICAL/CHEMICAL PROPERTIES OF THE 10 ALTERNATIVE PLASTICISERS EVALUATED TO BE POSSIBLE ALTERNATIVES TO DEHP IN MEDICAL DEVICES. DEHP IS INCLUDED FOR COMPARISON.

NOTES TO TABLE: THE INHERENT PROPERTIES OF THE 10 ALTERNATIVE PLASTICISERS ARE SUMMARISED FOR KEY PARAMETERS: PBT ASSESSMENT, BIODEGRADABILITY, WATER SOLUBILITY, LOG KOW, VAPOUR PRESSURE (PA), KH (PA M3/MOL) AND KOC.

Substance	CAS	Algae	Crustaceans	Fish	Terrestrial
DEHP	117-81-7	EC50: >0.003 mg/L	EC0: 101.8-165.65 µg/L* NOEC: 0.158 mg/L*	LC50: >0.16 mg/L* NOEC: 5000 µg/L*	Plants: NOEC: 100 mg/kg soil dw Macroorganisms: LC50: >1000 mg/kg soil dw
ASE	91082-17-6	EC0: >=2 mg/L	EC0: >=100 mg/L*	LC50: >=2 mg/L	-
ATBC	77-90-7	EC50: 74.4 mg/L*	EC50: >1 mg/L NOEC: >=1.11 mg/L	LC50: >38 and <60 mg/L*	-
BTHC	82469-79-2	NOEC: 1.04 mg/L	EC50: 0.38 mg/L	LC50: >120 mg/L	-
COMGHA	736150-63-3	EC50: 106 mg/L*	EC50: 0.92 mg/L* NOEC: >=70 µg/L	LC50: >0.28 mg/L NOEC: 32.1 µg/L	Plants: EC50: 12.5 mg/kg soil dw Macroorganisms: LC50: >1000 mg/kg soil dw
DEHT	6422-86-2	EC50: >0.86 mg/L*	EC50: >1.4 µg/L* NOEC: >= 0.76 µg/L*	LC50: >984 mg/L* NOEC: >=0.28 mg/L*	Plants: EC50: >1400 µg/L
DINA	33703-08-1	EC50: >100 mg/L*	EC50: >100 mg/L* NOEC: >=0.77 mg/L*	LC50: >500 mg/L*	Macroorganisms: LC50: 865 mg/kg soil dw
DINCH	166412-78-8	EC50: >100 mg/L*	EC50: >100 mg/L* NOEC: >=0.021 mg/L*	LC50: >100 mg/L*	Plants: EC50: > 1000 mg/kg soil dw Macroorganisms: LC50: >1000 mg/kg
DOA	103-23-1	EC50: >500 mg/L	EC50: > 500 mg/L	LC0: > 0.78 mg/L	Macroorganisms:

Substance	CAS	Algae	Crustaceans	Fish	Terrestrial
			NOEC: >=0.77 mg/L		LC50: >1000 mg/kg soil dw
ESBO	8013-07-08	EC50: 8 mg/L	EC50: >100 mg/L	LC50: 900 mg/L	-
TOTM/TEHTM	3319-31-1	EC50: >100 mg/L	EC50: >180 mg/L NOEC: 55.6 mg/L	LC50: >100 mg/L NOEC: >75 mg/L	Plants: LC50: >100 mg/kg soil dw Macroorganisms: LC10: >1000 mg/kg soil dw

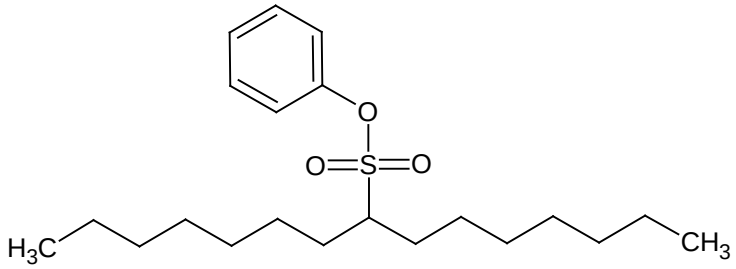
TABLE 6
OVERVIEW OF THE MAIN ECOTOXICOLOGICAL AND PHYSICAL/CHEMICAL PROPERTIES OF THE 10 ALTERNATIVE PLASTICISERS EVALUATED TO BE POSSIBLE ALTERNATIVES TO DEHP IN MEDICAL DEVICES. DEHP IS INCLUDED FOR COMPARISON.

NOTES TO TABLE: THE INHERENT PROPERTIES OF THE 10 ALTERNATIVE PLASTICISERS ARE SUMMARISED FOR KEY PARAMETERS: LC50, LC10, EC50, NOEC FOR ALGAE, CRUSTCEANS, FISH AND THE TERRESTRIAL ENVIRONMENT.

Appendix 4: Data sheets for the alternatives

Sulfonic acids, C10-21-alkane, Ph esters (ASE)

Identification of substance

CAS No.	91082-17-6
EINECS No.	293-728-5
IUPAC name	Sulfonic acids, C10-C21-alkane, Ph-esters
Structure	
SMILES	O=S(=O)(Oc1ccccc1)C(CCCCCCC)CCCCCCC

REACH

Registration	Full
Submission	Individual Submission
Total tonnage	10,000 - 100,000 tonnes per annum
Harmonised classification	Not classified
Notified classification	Not classified
REACH registration classification	Not classified
Wide dispersive end use opened/closed	Yes
Wide dispersive end use closed	No
Wide dispersive service life opened/closed	Yes
Wide dispersive service life closed	No

Physical-chemical characteristics

Molecular weight	- g/mole
Vapour pressure	0.000294 Pa, 20 °C (OECD Guideline 104) Klimisch score: 1
Henry's law constant	0.04 - 0.061 Pa m^3/mol, 20 °C (The Henry's law constant (HLC) is directly calculated as a ratio of the vapour pressure to the water solubility) Klimisch score: 2
Water solubility	2.2 mg/L, 20 °C (OECD Guideline 105) Klimisch score: 1
Log K_{ow}	5.7 - 11.3, 40 °C (OECD Guideline 117) Klimisch score: 1

Toxicological data

Acute toxicity	LD50 (oral) > 15 mL/kg bw - Klimisch score 2 (key study) LD50 (dermal) > 1055 mg/kg bw - Klimisch score 2 (key study) LC50 (inhalation): No data
Irritation and sensitation	No skin irritation or corrosive effects (human patch test - no guideline) No skin irritation (rabbit - no guideline) - Klimisch score 2 (key study) No eye irritation (rabbit - no guideline) - Klimisch score 2 (key study)
Sensitation	No skin sensitization (Guinea Pig Maximization Test -OECD 406) Klimisch score: 1 (key)
Repeated toxicity	NOAEL 3000 ppm (90 day - OECD 408) (males: 228.0 mg/kg bw./day; females: 282.6 mg/kg bw./day) LOAEL =12000 ppm (Kidney weight and increased tromboplastin-time) (males: 985.2 mg/kg bw./day; females: 1488.5 mg/kg bw./day) Klimisch score 1 (key study)
Mutagenicity/genotoxicity	Negative in the V79 -HPRT Forward Mutation Assay (+/- metabolic activation) (No guideline) - Klimisch score 2 (key study) Negative in the vitro Mammalian Chromosome Aberration Test (+/- metabolic activation) (OECD Guideline 473) - Klimisch score 2 (key study) Negative in the bacterial reverse mutation assay (No guideline) - Klimisch score 2 (key study)
Endocrine	No data
Carcinogenicity	No data
Reproductive and developmental toxicity	Reproductive toxicity – one generation reproduction (OECD 415): NOAEL (parental toxicity) 600 ppm (68 mg/kg bw/day*), LOAEL 3000 ppm (liver/kidney weight) NOAEL (reproduction) 600 ppm (68 mg/kg bw/day*), LOAEL 3000 ppm (fetal weight/development – balano seperation), LOAEL 15000 ppm (vaginal opening) Klimisch score 1 (key study) Developmental toxicity (OECD 414): NOAEL (maternal toxicity) 300 mg/kg bw/day; LOAEL 1000 mg/kg bw/day (body weight gain) NOAEL (developmental toxicity) = 1000 mg/kg bw/day (highest dose level) Klimisch score 1 (key study)
Toxicokinetics/Metabolism	The half-life in fat tissue after single oral application and repeated oral application of 1000 mg/kg was 8 days and 15 days, respectively. No accumulation was observed in the liver. 20 - 30 % of the dose was excreted in the faeces within 24 h. Klimisch score 2 (key study)

Other	Cytotoxicity: No data Hemocompability: No data
DNEL (W) oral	No data
DNEL (W) inhalation	6.5 mg/m³ (long-term); 84.8 mg/m³ (acute)
DNEL (W) dermal	6.5 mg/m³ (long-term); 84.8 mg/m³ (acute)
DNEL (G) oral	0.47 mg/kg bw/day (long-term
DNEL (G) inhalation	No data
DNEL (G) dermal	0.47 mg/kg bw/day (long-term)

Ecotoxicological data

Algae	EC0 (*Desmodesmus subspicatus*, 72 hours): >=2 mg/L (EU Method C.3 (Algal Inhibition test)) Klimisch score: 1
Crustaceans	EC0 (*Daphnia magna*, 48 hours): >=100 mg/L* (EU Method C.2 (Acute Toxicity for Daphnia)) Klimisch score: 1
	-
Fish	LC0 (*Danio rerio*, 96 hours): >=2 mg/L (EU Method C.1 (Acute Toxicity for Fish)) Klimisch score: 1
	-
Terrestrial plants	-
Soil macroorganisms	-
PNEC (fresh water)	0.002 mg/L (Assessment factor: 1000)
PNEC (marine water	0.0002 mg/L (Assessment factor: 10000)
PNEC (fresh water sediment)	10.03 mg/kg sediment dw

PNEC (marine water sediment)	1 mg/kg sediment dw
PNEC (soil)	2 mg/kg soil dw (Assessment factor: -)

Environmental fate

Bioconcentration factor (BCF)	7 - 212 (-) Klimisch score: 1
Ready biodegradability	C10-21-alkane, Ph esters is not readily biodegradable, but is degradable as the pass level of 60 % degradation (BOD) was achieved after 47 days (EU Method C.4-D) Klimisch score: 1
Adsorption/desorption	log Koc: 4.5 - 9.3 (PCKOC and other calculation methods) Klimisch score: 2

PBT

REACH registration dossier	-
QSAR	P: Neg; B: Pos; T: - ; BCF: 790 Fish ChV (mg/L): - Half-life (Water, days): 38 Half-life (Soil, days): 75 Half-life (Sediment, days): 340 Half-life (Air, days): 0.75

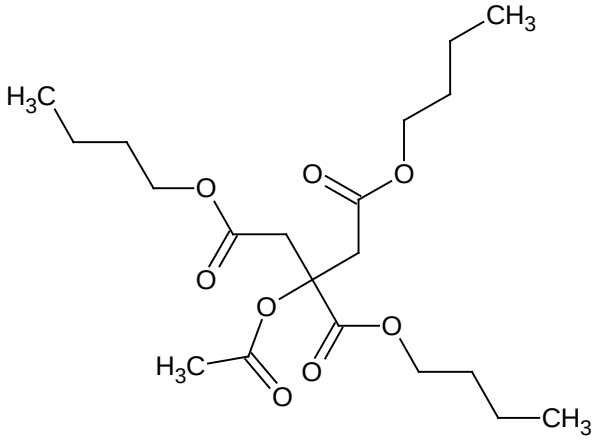
QSAR bioavailability

Lipinski	Not bioavailable
Mammalian metabolism	
Microbial metabolism (observed)	ND
Microbial metabolism (simulated)	69 metabolites formed. Of these: 69 bioavailable and 0 not bioavailable. Monoesters formed.
Rat In vivo metabolism (observed)	ND
Rat In vivo metabolism(simulated)	
Rat Liver S9 metabolism (observed)	ND
Rat Liver S9 metabolism (simulated)	ND
Skin metabolism	2 metabolites formed. Of these: 2 bioavailable and 0 not bioavailable. Monoesters formed.

*Identified from the reference “Analysis of Alternatives (non-confidential report), Hazard and risk evaluation of DEHP alternatives prepared on behalf of the DEHP authorization task force (ATF), June 2013 – ARKEMA, France”.

tributyl O-acetylcitrate (ATBC)

Identification of substance

CAS No.	77-90-7
EINECS No.	201-067-0
IUPAC name	tributyl 2-acetoxypropane-1,2,3-tricarboxylate
Structure	
SMILES	O=C(OC(C(=O)OCCCC)(CC(=O)OCCCC)CC(=O)OCCCC)C

REACH

Registration	Full
Submission	Joint Submission
Total tonnage	1,000 - 10,000 tonnes per annum
Harmonised classification	Not classified
Notified classification	Not classified
REACH registration classification	Not classified
Wide dispersive end use opened/closed	Yes
Wide dispersive end use closed	No
Wide dispersive service life opened/closed	No
Wide dispersive service life closed	No

Physical-chemical characteristics

Molecular weight	402.49 g/mole
Vapour pressure	0.0494 Pa, 25 °C (EPISUITE 4.00 (MPBPVP v1.43), Modified Grain method) Klimisch score: 2
Henry's law constant	4.434 Pa m^3/mol, 25 °C (EPIWIN (v4.0), HENRYWIN (v 3.20)) Klimisch score: 2
Water solubility	4.49 mg/L, 20 °C, pH 6.7 -6.8 (EU Method A.6 (Water Solubility)) Klimisch score: 1
Log K_{ow}	4.86, 40 °C, pH 7.1 (EPA OPPTS 830.7570) Klimisch score: 1

Toxicological data

Acute toxicity	LD50 (oral) > 30 mL/kg (ca. 31500 mg/kg) - Klimisch score 2 (key study) LD50 (dermal) > 1000 mg/kg bw - Klimisch score 2 (key study) LC50 (inhalation): No data
Irritation and sensitation	No skin irritation (rabbit-no guideline) - Klimisch score 2 (key study) Slightly eye irritation (rabbit-no guideline) - Klimisch score 2 (key study)
Sensitation	No skin-sensitization potential (guinea pigs-OECD 406) - Klimisch score 4 (only summary - WOE) No skin-sensitization or irritation potential (human - patch test) - Klimisch score 4 (only summary - WOE)
Repeated toxicity	NOAEL 1000 mg/kg bw/day (male/female) (90 day in diet - OECD 408) (highest dose level - slightly increased liver weights accompanied by minimal hepatocellular hypertrophy) - Klimisch score 1 (key study) NOAEL 300 mg/kg bw/day (male/female) (52 weeks in diet - comparable to OECD 452), LOAEL 1000 mg/kg bw/day (increased liver weight and centrilobular hypertrophy) - Klimisch score 1 (key study)
Mutagenicity/genotoxicity	Negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (OECD 471) - Klimisch score 2 (key study) Negative in mammalian cell gene mutation assay (+/- metabolic activation) (OECD 476) - Klimisch score 2 (supporting study) Negative in *in vivo* chromosome aberration assay (rat) (OECD Guideline 475) - Klimisch score 1 (key study)
Endocrine	No data
Carcinogenicity	NOEL 1000 mg/kg bw/day (no neoplastic lesions in male/female) (104 wk. In diet - combined repeated dose and carcinogenicity study - 875/318/EEC; 83/571/EEC; 91/507/EEC guideline - comparable to OECD 452) Klimisch score 1 (Key study)
Reproductive and developmental toxicity	Reproductive toxicity: No data Developmental toxicity (no guideline –mice and rats treated 12 months-cross mating): NOEL (maternal toxicity) 50 mg/kg bw/day LOAEL (maternal toxicity) 250 mg/kg bw/day (body weight increase, length of the progeny and placental weight) NOEL (developmental toxicity) 250 mg/kg bw/day (highest dose level) (no effects to male sexual cells, no embryotoxic effects and no impact on the development in offspring) - Klimisch score 2 (key studies)

Toxicokinetics/Metabolism	After oral gavage in an ADME study, ATBC is rapidly absorbed, metabolized and excreted by rats. No bioaccumulation potential based on study results. The low oral toxicity of ATBC is not due to poor absorption but is caused by an intrinsic property of ATBC and/or its metabolites or is due to rapid clearance in the rat. After oral gavage, ATBC is rapidly absorbed, metabolized and excreted by rats. (no guideline but comparable to OECD 417) - Klimisch score 1 (Key study)
Other	Cytotoxicity: No data Hemocompability: No data
DNEL (W) oral	No data
DNEL (W) inhalation	7.04 mg/m³ (long-term)
DNEL (W) dermal	2 mg/kg bw/day (long-term)
DNEL (G) oral	1 mg/kg bw/day (long-term)
DNEL (G) inhalation	1.74 mg/m³ (long-term)
DNEL (G) dermal	1 mg/kg bw/day (long-term)

Ecotoxicological data

Algae	EC50 (*Desmodesmus subspicatus*, 72 hours): 74.4 mg/L* (OECD Guideline 201) Klimisch score: 1
Crustaceans	EC50 (*Daphnia magna*, 24 hours): >1 mg/L (OECD Guideline 202) Klimisch score: 2 NOEC (*Daphnia magna*, 21 days): >=1.11 mg/L (EU Method C.20 (Daphnia magna Reproduction Test)) (WOE) Klimisch score: 1
Fish	LC50 (*Lepomis macrochirus*, 96 hours): >38 and <60 mg/L* (OECD Guideline 203) Klimisch score: 2
	-
Terrestrial plants	-

Soil macroorganisms	-
PNEC (fresh water)	0.022 mg/L (Assessment factor: 50)
PNEC (marine water	0.0022 mg/L (Assessment factor: 500)
PNEC (fresh water sediment)	41.5 mg/kg sediment dw
PNEC (marine water sediment)	4.15 mg/kg sediment dw
PNEC (soil)	8.29 mg/kg soil dw (Assessment factor: -)

Environmental fate

Bioconcentration factor (BCF)	31.57 (BCFBAF Program (v 3.00)) Klimisch score: 2
Ready biodegradability	inherently biodegradable Klimisch score: 2
Adsorption/desorption	log Koc: 4.271 (OECD Guideline 121) Klimisch score: 1

PBT

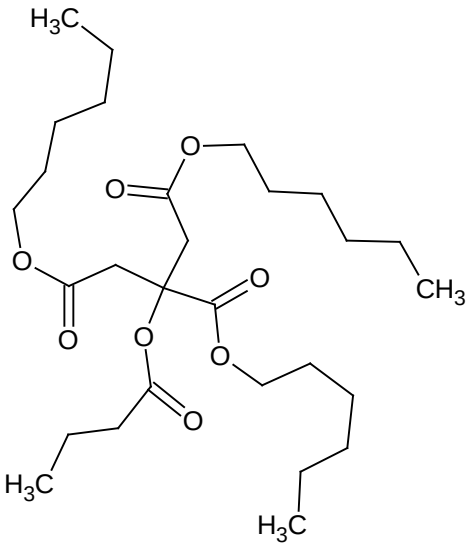
REACH registration dossier	The substance is not PBT / vPvB
QSAR	P: Neg; B: Neg; T: Pos; BCF: 13 Fish ChV (mg/L): 0.12 Half-life (Water, days): 8.7 Half-life (Soil, days): 17 Half-life (Sediment, days): 78 Half-life (Air, days): 1.1

QSAR bioavailability

Lipinski	Bioavailable
Mammalian metabolism	
Microbial metabolism (observed)	ND
Microbial metabolism (simulated)	41 metabolites formed. Of these: 40 bioavailable and 1 not bioavailable. Monoesters formed.
Rat In vivo metabolism (observed)	5 metabolites formed. Of these: 5 bioavailable and 0 not bioavailable. Monoesters formed.
Rat In vivo metabolism(simulated)	
Rat Liver S9 metabolism (observed)	ND
Rat Liver S9 metabolism (simulated)	11 metabolites formed. Of these: 11 bioavailable and 0 not bioavailable. Monoesters formed.

BTHC (butyl trihexyl citrate)

Identification of substance

CAS No.	82469-79-2
EINECS No.	-
IUPAC name	-
Structure	
SMILES	O=C(CC(CC(=O)OCCCCCC)(C(=O)OCCCCCC)OC(=O)CCC)OCCCCCC

REACH

Registration	-
Submission	-
Total tonnage	-
Harmonised classification	-
Notified classification	-
Wide dispersive end use opened/closed	-
Wide dispersive end use closed	-
Wide dispersive service life opened/closed	-
Wide dispersive service life closed	-

Physical-chemical characteristics

Molecular weight	514.70 g/mole (Vertellus MSDS)
Vapour pressure	<0.000001 Pa (Vertellus MSDS)
Henry's law constant	3.70×10^{-4} Pa m^3/mol (EPIWEB 4.1)
Water solubility	0.61 mg/L, 20°C, pH 6 (Vertellus MSDS)
Log K_{ow}	8.21 (EPIWEB 4.1)

Toxicological data*

Acute toxicity	LD50 (oral) > 5000 mg/kg bw/day (rat, no guideline - standard acute method) LD50 (dermal) > 2000 mg/kg bw/day (rabbit, occlusive - no guideline) LC50 (inhalation): No data Klimisch score: key studies
Irritation and sensitation	No skin irritation (rabbit, occlusive-no guideline) No eye irritation (rabbit - no guideline) Klimisch score: key studies
Sensitation	No skin-sensitization potential (guinea pigs-no guideline) No skin-sensitization potential (guinea pigs-no guideline) Klimisch score: key studies
Repeated toxicity	NOEL 250 mg/kg bw/day (nominal) - (28 day, rat, oral - No guideline) (liver weight changes and changes in blood parameters) NOEL 50 mg/kg bw/day - (18 day, neonatal rat, iv and ip - no guideline) (liver weight changes (ip), some histopathological changes in the lung (iv)) NOEL 50 mg/kg bw//day - (28 day, rat, iv - No guideline) (liver and spleen weight changes, changes in blood parameters) Klimisch score: key studies No hepatic peroxisome proliferation in rats given 3% in the diet for six weeks (no guideline) - Klimisch score: key study
Mutagenicity/genotoxicity	Negative/positive in *in vitro* Mammalian Chromosome Aberration (+/- metabolic activation) (no guideline) - Klimisch score: key study Negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (no guideline) - Klimisch score: key study Negative in mammalian cell gene mutation assay (+/- metabolic activation) (OECD 476) - Klimisch score: key study Negative in *in vivo* micronucleus assay (1000 mg/kg bw/day – 1 to 5 days) (no guideline) – Klimisch score: key study
Endocrine	No data
Carcinogenicity	No data. However BHTC is neither genotoxic nor is it a peroxisome proliferating agent - Klimisch score: WOE
Reproductive and developmental toxicity	Reproductive toxicity – (one generation reproduction study – no guideline): A one-generation fertility study was carried out in albino rats at dietary levels of 0,0.6 0r 1.2% BTHC. No effects on fertility and other reproductive indices, or on litter weights and pup weights. No increase in abnormalities in the F1 pups was found - - Klimisch score: key study Developmental toxicity – (no guideline):

	NOEL (developmental toxicity) 500 mg/kg bw/day (highest tested dose level) Klimisch score: key study
Toxicokinetics/Metabolism	BTHC is well absorbed after oral administration. It is rapidly metabolised by hydrolysis of the ester bonds to a number of metabolites. The principal metabolite is n-hexanol. There are no structural alerts for any of the metabolites. Radiolabelled BTHC is cleared rapidly from the body following iv administration through a combination of urinary and biliary excretion and expired air. BTHC related material does not accumulate in any of the body tissues. The clearance is biphasic with half-lives of <15 minutes and >24hours. The latter half-life indicates that the radiolabel is widely incorporated into intermediary metabolism pathways. The findings indicate that BTHC is unlikely to accumulate in the body even after a prolonged period of exposure. Klimisch score: key study
Other	

Ecotoxicological data

Algae	NOEC (72 hours, *selenatrum capricortnum*): 1.04 mg/L (Vertellus MSDS)
Crustaceans	EC50 (48 hours, *daphnia magna*): 0.38 mg/L (Vertellus MSDS)
	-
Fish	LC50 (96 hours, *oncorhynchus mykiss*): >120 mg/L (Vertellus MSDS)
	-
Terrestrial plants	-
Soil macroorganisms	-
PNEC (fresh water)	-
PNEC (marine water	-
PNEC (fresh water sediment)	-
PNEC (marine water sediment)	-
PNEC (soil)	-

Environmental fate

Bioconcentration factor (BCF)	log BCF: 2.93 (EPIWEB 4.1)
Ready biodegradability	Not meeting the conditions of ready biodegradable (Vertellus MSDS)
Adsorption/desorption	
	log Koc: 7.0478 (EPIWEB 4.1)

PBT

REACH registration dossier	
QSAR	P: Pos; B: Neg; T: -; BCF: 860
	Fish ChV (mg/L): -
	Half-life (Water, days): 8.7
	Half-life (Soil, days): 17
	Half-life (Sediment, days): 78
	Half-life (Air, days): 0.67

QSAR bioavailability

Lipinski	Not bioavailable
Mammalian metabolism	
Microbial metabolism (observed)	ND
Microbial metabolism (simulated)	58 metabolites formed. Of these: 27 bioavailable and 31 not bioavailable. Monoesters formed.
Rat In vivo metabolism (observed)	ND
Rat In vivo metabolism(simulated)	
Rat Liver S9 metabolism (observed)	ND
Rat Liver S9 metabolism (simulated)	14 metabolites formed. Of these: 11 bioavailable and 3 not bioavailable. Monoesters formed.
Skin metabolism	29 metabolites formed. Of these: 16 bioavailable and 13 not bioavailable. Monoesters formed.

*No registration dossier available, data has been extracted from SCENIHR 2008 (Opinion on the safety of medical devices containing DEHP plasticised PVC or other plasticisers on neonates and other groups possibly at risk).

COMGHA

Identification of substance

CAS No.	736150-63-3
EINECS No.	451-530-8
IUPAC name	-
Structure	N/A
SMILES	-

REACH

Registration	Full
Submission	Individual Submission
Total tonnage	1,000 - 10,000 tonnes per annum
Harmonised classification	Not classified
Notified classification	Not classified
REACH registration classification	Not classified
Wide dispersive end use opened/closed	Yes
Wide dispersive end use closed	No
Wide dispersive service life opened/closed	Yes
Wide dispersive service life closed	No

Physical-chemical characteristics

Molecular weight	- g/mole
Vapour pressure	0.000000048 Pa, 20 °C (OECD Guideline 104) Klimisch score: 1
Henry's law constant	-
Water solubility	< 0.33 mg/L, 20 °C, pH 6.8 (OECD Guideline 105) Klimisch score: 1
Log K_{ow}	6.4, 25 °C (OECD Guideline 117) Klimisch score: 2

Toxicological data

Acute toxicity	LD50 (oral) > 2000 mg/kg bw/day – (no guideline) - Klimisch score 1 (key study) LD50 (dermal) > 2000 mg/kg bw/day (OECD 402) - Klimisch score 1 (key study) LC50 (inhalation): No data
Irritation and sensitation	No skin irritation (rabbit-OECD 404) - Klimisch score 1 (key study) No eye irritation (rabbit-OECD 405) - Klimisch score 1 (key study)

Sensitation	No skin-sensitization potential (mice-OECD 429) - Klimisch score 1 (key study)
Repeated toxicity	NOAEL >= 1333 mg/kg bw/day (male/female) - (12 months in diet - OECD 452) (highest dose level) - Klimisch score 1 (key study) NOAEL > 5000 mg/kg bw/day (male/female) - (90 days in diet - OECD 408) (highest dose level) - Klimisch score 1 (key study)
Mutagenicity/genotoxicity	Negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (OECD 471) - Klimisch score 1 (key study) Negative in *in vitro* mammalian chromosome aberration test (+/- metabolic activation) (OECD Guideline 473) - Klimisch score 1 (key study) Negative in mammalian cell gene mutation assay (+/- metabolic activation) (OECD Guideline 476) - Klimisch score 1 (key study) Negative in *in vivo* micronucleus assay (mice) (OECD 474) - Klimisch score 1 (key study)
Endocrine	Endpoints included in a combined two-generation reproductive and developmental neurotoxicity study (rat - OECD 416 and 426) - Klimisch score 1 (key study) No antiandrogenic effects (reduced anogenital distance, retained nipples, cleft phallus, hypospadias, undescended testes, blind vaginal pouch, epididymal agenesis, underdeveloped accessory sex glands, delay in puberty and histological alterations in the testes). Further, the sexual differentiation was unaffected in male offspring. No developmental neurotoxicity in the offspring
Carcinogenicity	No data. Data waiving based on data of low concern on repeated dose toxicity and mutagenicity.
Reproductive and developmental toxicity	Reproductive toxicity - combined two-generation reproductive and developmental neurotoxicity study (rat - OECD 416 and 426): No effects on reproduction and pre-/post-natal development when administered to two successive generations using 1500, 6000 or 25000 ppm in the diet. NOEL for adult toxicity and reproduction over the two generations was 25000 ppm (at least 1000 mg/kg bw/day throughout all of the study) A NOAEL of 25000 ppm for offspring development and a NOEL for offspring survival, growth and developmental neurotoxicity was identified (at least 1000 mg/kg bw/day throughout all of the study). The mean achieved dosages at this exposure level were 1159 mg/kg bw/day (F0 male), 2200 mg/kg bw/day (F0 female), 1320 mg/kg bw/day (F1 male) and 2262 (F1 female). The lowest identified NOAEL at exposure level 25000 ppm was ≥ 1159 mg/kg bw/day (F0 male) (highest dose level) - Klimisch score 1 (key study). Developmental toxicity (rat - OECD 414):

	NOEL (maternal toxicity) = 1000 mg/kg bw/day NOEL (developmental toxicity) = 1000 mg/kg bw/day Highest dose level - Klimisch score 1 (key study) Developmental toxicity (rabbit - OECD 414): NOEL (maternal toxicity) = 1000 mg/kg bw/day NOEL (developmental toxicity) = 1000 mg/kg bw/day Highest dose level - Klimisch score 1 (key study)
Toxicokinetics/Metabolism	Toxicokinetics (rat - OECD 417): Uptake of radioactivity (12-[1-14C]acetoxy-octadecanoic acid-2,3- diacetoxy-propyl ester) into the systemic circulation was rapid with a peak concentration (representing <2% of the dose) in blood occurring within 6 hours post-dosing. Elimination of radioactivity from the blood was slow at both doses. The mean plasma elimination half-life was between 51.9-55.6 hours. Radioactivity was eliminated from the body as 14C-CO2 with 62% accounted for within 12 hours of dosing, 70.8% within 24 hours and 77% after 72 hours. The remaining radioactivity was excreted in urine (6.5%) and faeces (24.6%). Conclusion: Metabolism is expected to be rapid with extensive hydrolytic cleavage of the 12-acetyl function from labelled TS-ED 532 and subsequent catabolism of the majority of the released 14-C labelled acetate to 14C-CO2. Klimisch score 1 (key study)
Other	Non-cytotoxic to cell culture (L929 cells) (BS-EN ISO 10993-5) (data supplied from manufacturer) Non-haemolytic to human blood (BS-EN ISO 10993-4) (data supplied from manufacturer)
DNEL (W) oral	No data (no critical effects identified)
DNEL (W) inhalation	No data (no critical effects identified)
DNEL (W) dermal	No data (no critical effects identified)
DNEL (G) oral	No data (no critical effects identified)
DNEL (G) inhalation	No data (no critical effects identified)
DNEL (G) dermal	No data (no critical effects identified)

Ecotoxicological data

Algae	EC50 (*Selenastrum capricornutum*, 72 hours): 106 mg/L* (OECD Guideline 201) Klimisch score: 1
Crustaceans	EC50 (*Daphnia magna*, 48 hours): 0.92 mg/L* (OECD Guideline 202) Klimisch score: 1

	NOEC (*Daphnia magna*, 21 days): >=70 µg/L (OECD Guideline 211) Klimisch score: 1
Fish	LC50 (*Danio rerio*, 96 hours): >0.28 mg/L (OECD Guideline 203) Klimisch score: 1
	NOEC (*Danio rerio*, 67 days): 32.1 µg/L (OECD Guideline 210) Klimisch score: 1
Terrestrial plants	EC50 (*Hordeum vulgare*, 22 days): 12.5 mg/kg soil dw (OECD Guideline 208) Klimisch score: 1
Soil macroorganisms	LC50 (*Eisenia fetida*, 14 days): >1000 mg/kg soil dw (OECD Guideline 207) Klimisch score: 1
PNEC (fresh water)	5 µg/L (Assessment factor: 10)
PNEC (marine water	5 µg/L (Assessment factor: 100)
PNEC (fresh water sediment)	28 mg/kg sediment dw
PNEC (marine water sediment)	2.8 mg/kg sediment dw
PNEC (soil)	0.02 mg/kg soil dw (Assessment factor: 100)

Environmental fate

Bioconcentration factor (BCF)	981 (OECD Guideline 305) Klimisch score: 1
Ready biodegradability	readily biodegradable (OECD Guideline 301 F) Klimisch score: 1
Adsorption/desorption	log Koc: 5.4, 25 °C (OECD Guideline 121) Klimisch score: 1

PBT

REACH registration dossier	-
QSAR	P: -; B: -; T: -; BCF: -

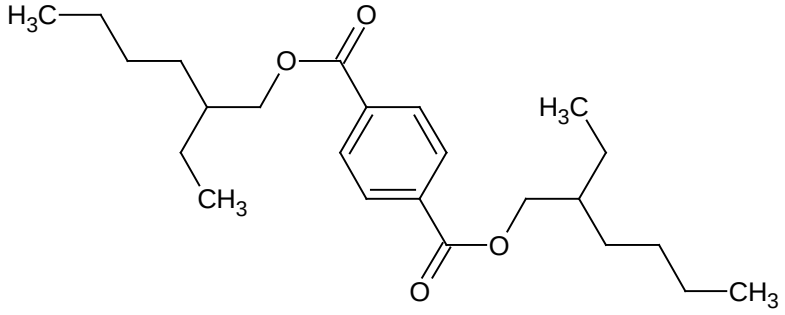
Fish ChV (mg/L): -
Half-life (Water, days): -
Half-life (Soil, days): -
Half-life (Sediment, days): -
Half-life (Air, days): -

QSAR bioavailability

Lipinski	ND
Mammalian metabolism	ND
Microbial metabolism (observed)	ND
Microbial metabolism (simulated)	ND
Rat In vivo metabolism (observed)	ND
Rat In vivo metabolism(simulated)	ND
Rat Liver S9 metabolism (observed)	ND
Rat Liver S9 metabolism (simulated)	ND
Skin metabolism	ND

DEHT bis(2-ethylhexyl) terephthalate

Identification of substance

CAS No.	6422-86-2
EINECS No.	229-176-9
IUPAC name	bis(2-ethylhexyl) terephthalate
Structure	
SMILES	O=C(OCC(CCCC)CC)c(ccc(c1)C(=O)OCC(CCCC)CC)c1

REACH

Registration	Full
Submission	Joint Submission
Total tonnage	10,000 - 100,000 tonnes per annum
Harmonised classification	Not classified
Notified classification	Not classified
REACH registration classification	Not classified
Wide dispersive end use opened/closed	Yes
Wide dispersive end use closed	Yes
Wide dispersive service life opened/closed	Yes
Wide dispersive service life closed	No

Physical-chemical characteristics

Molecular weight	390.57 g/mole
Vapour pressure	< 0.001 Pa, 25 °C (EU Method A.4 (Vapour Pressure)) Klimisch score: 2
Henry's law constant	-
Water solubility	ca. 0.4 µg/L, 22.5 °C, pH ca. 5 (Method Reference: Ellington, JJ, 1999, J. Chem. Eng. Data, 44, 1414-1418) Klimisch score: 2
Log K_{ow}	7.81, 25 °C, pH 7 (QSAR (SPARC) used and acceptable in accordance with REACH Annex XI) (WOE) Klimisch score: 2

Toxicological data

Acute toxicity	LD50 (oral, rat) > 5000 mg/kg bw/day (other guideline comparable to OECD) Klimisch score 1 (key study)
	LD50 (dermal, guinea pigs) > 20000 mg/kg bw) (No guideline) Klimisch score 2 (key study)
	LC50 (inhalation): No data
	LD50 (ip, rat): > 3200 mg/kg bw (No guideline) Klimisch score 2 (supporting study)
	LD50 (ip, mice): > 3200 mg/kg bw (No guideline) Klimisch score 2 (supporting study)
Irritation	No skin irritation (rabbit-OECD 404) - Klimisch score 1 (key study) No skin irritation (human patch test - semi-occlusion) - Klimisch score 1 (key study)
	Skin irritation (guinea pigs - no guideline) (undiluted under occlusive wrap for 24 hours) - Klimisch score 2 (supporting study)
	Mildly eye irritating but not classified under GHS (rabbit-OECD 405) - Klimisch score 1 (key study)
Sensitation	No skin-sensitization potential (Human patch test -modified Draize procedure) Klimisch score 1 (key study)
	No skin-sensitization potential (guinea pigs - topical application - no guideline) Klimisch score 2 (supporting study)
Repeated toxicity	NOEL 0.5% in diet (277 mg/kg bw/day (male) and 309 mg/kg bw/day (female)) LOAEL 1% (561 mg/kg bw/day (male) and 617 mg/kg bw/day (female) - minor effects on red blood cell formation and enlargement of the liver) (90 days-EPA guideline 799.9310 TSCA) - Klimisch score 1 (key study)
	NOEL 1500 ppm (79/102 mg/kg/day - M/F) LOEL 6000 ppm (324/418 mg/kg/day – M/F, reduced body weight gain, food conversion efficiency, minor haematological effects, suspected ocular changes) NOEL 12000 ppm (666/901 mg/kg/day - M/F) -testes NOEL 12000 ppm (666/901 mg/kg/day - M/F) - liver (Chronic toxicity-EPA OPPTS 870.4200) - Klimisch score 1 (key study)
Mutagenicity/genotoxicity	Negative in *in vitro* Mammalian Chromosome Aberration Test (+/- metabolic activation) (OECD 473) - Klimisch score 1 (key study)
	Negative *in vitro* in Bacterial Reverse Mutation Assay (+/- metabolic activation)

	(OECD 471) - Klimisch score 1 (key study) Negative *in vitro* in mammalian cell gene mutation assay (+/- metabolic activation) (OECD 476) - Klimisch score 1 (key study) Urine samples from rats given 2000 mg/kg bw/day for 15 days were negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (OECD 471). Klimisch score 2 (supporting study)
Endocrine	Uterotrophic Assay (no guideline followed): Immature female Sprague-Dawley rats dosed by gavage once daily from postnatal days 19 through 21 at dose levels of 0, 20, 200 and 2000 mg/kg bw/day. No test substance related differences in mean uterine weights (wet or blotted) or luminal fluid weights. No biological activity consistent with agonism of natural oestrogens at dose levels up to 2000 mg/kg bw/day. Klimisch score 2 (key study) Pregnant rats were exposed to 0.75 g/kg bw/day (oral gavage) from gestation day 14 to postnatal day 3 in a modified developmental toxicity study (no guideline followed – OECD 414 normally start dosing at gestation day 6 or 7): Offspring were sacrificed at 4-7 months of age, body and selected organ weights were measured, and animals were examined for abnormalities. This study did not investigate many of the endpoints normally measured in standard (Guideline) developmental/teratology studies; instead, endpoints specific to androgen disruption (reduced anogenital distance, retained nipples, cleft phallus, hypospadias, undescended testes, blind vaginal pouch, epididymal agenesis, underdeveloped accessory sex glands, and histological alterations in the testes) were investigated. No effect in male offspring on the endpoints specific to androgen disruption and sexual differentiation. Klimisch score 1 (supporting study) Pregnant Sprague-Dawley rats were exposed from gestation day 12 through gestation day 19 to 500 mg/kg bw/day (no guideline followed): Anogenital distance was not significantly altered in male foetuses and none of the genes representing major gene pathways that allow for normal male reproductive tract development were altered. Klimisch score 1 (supporting study)
Carcinogenicity	104 week carcinogenicity study in rat using dose levels of 1500 ppm (79/102 mg/kg/day - M/F), 6000 ppm (324/418 mg/kg/day - M/F) and 12000 ppm (666/901 mg/kg/day - M/F) (EPA OPPTS 870.4200) NOEL 12000 ppm (666/901 mg/kg/day - M/F – no neoplastic changes) Klimisch score 1 (key study)
Reproductive and developmental toxicity	Reproductive toxicity (OECD 416, EPA OPPTS 870.3800 - two generation reproduction): NOAEL (parental toxicity) 3000 ppm (F0: 133-478 mg/kg bw/day for male-female, respectively) (F1: 159-516 mg/kg bw/day for male-female, respectively)

	LOAEL (parental toxicity) 6000 ppm (reduced body weight gain in parent/offspring) (F0: 265-940 mg/kg bw/day for male-female, respectively) (F1: 320-1036 mg/kg bw/day for male-female, respectively) NOAEL (reproduction) = 10000 ppm (447-1349 mg/kg bw/day for male-female, respectively) Klimisch score 1 (key study) Developmental toxicity - rat (Prenatal developmental toxicity - OECD 414, EPA OPPTS 870.3700): NOAEL (maternal toxicity) 6000 ppm (458 mg/kg bw/day) LOAEL (maternal toxicity) 10000 ppm (747 mg/kg bw/day - higher liver weights, reduced body weight/body weight gain) NOAEL (developmental toxicity) 10000 ppm (747 mg/kg bw/day) Klimisch score 1 (key study) Developmental toxicity - mice (Prenatal developmental toxicity OECD 414, EPA OPPTS 870.3700): NOEL (maternal toxicity) 1000 ppm (197 mg/kg bw/day) LOAEL (maternal toxicity) 3000 ppm (592 mg/kg bw/day - (increased liver weight) NOEL (developmental toxicity) 7000 ppm in diet (1382 mg/kg bw/day). Klimisch score 1 (key study)
Toxicokinetics/Metabolism	In vivo metabolism study (rat, oral - no guideline) with radiolabeled di(2-ethylhexyl) terephthalate: Most of the radioactivity was eliminated in the faeces (56.5 ± 12.1%) and urine (31.9 ± 10.9%), with smaller amounts in expired air (3.6 ± 0.9%). Approximately 1.4 ± 0.6% of the dose remained in the carcass. Metabolite analysis indicated that the major excretory products of di (2-ethylhexyl) terephthalate are terephthalic acid (TPA) and di (2-ethylhexyl) terephthalate, together accounting for 87.1% of the dose. Only a small percentage of the administered dose was excreted as mono-(2-ethylhexyl) terephthalate or its oxidative metabolites. Under the conditions of the study, di (2-ethylhexyl) terephthalate has a low potential for bioaccumulation and presents a low toxicity hazard. In vitro hydrolysis study (rat, oral - no guideline) with radiolabelled di (2-ethylhexyl) terephthalate incubated with rat intestinal homogenate: di (2-ethylhexyl) terephthalate was metabolized by enzymes present in the gut and that the hydrolysis followed first-order kinetics with a disappearance half-life of 53.3 minutes. This study provides evidence that, in vivo, di (2-ethylhexyl) terephthalate would undergo complete hydrolysis to yield terephthalic acid and 2-ethylhexanol which are rapidly eliminated. Skin absorption in vitro (OECD Guideline 428): Absorption rate (human skin) = 0.103 ± 0.052 µg/cm^2/hr. Mean damage ratio=1.14 ± 0.23. Low skin penetration potential and therefore limited systemic exposure from dermal application.

	(Dermal uptake scenario: estimation of 1.06 µg/kg di (2-ethylhexyl) terephthalate uptake following a continuous 1 hour dermal exposure in an area of skin equivalent to both hands (approximately 720 cm^2, 70-kg person)) Klimisch score: 1(key study); 2 (supporting study); 1(key study)
Other	Non-cytotoxic to cell culture (L929 cells) (BS-EN ISO 10993-5) (data supplied from manufacturer)
	Non-haemolytic to rabbit blood (ISO/IEC 17025) (data supplied from manufacturer)
	Systemic injection test (mice): No signs of toxicity Intracutaneously test (rabbit): No signs of toxicity (US Pharmacopeia and ISO/IEC 17025) (data supplied from manufacturer)
	Blood bags formulated with DEHT: No negative effects on storage parameters of erythrocyte parameters. (data supplied from manufacturer)
DNEL (W) oral	No data
DNEL (W) inhalation	23.2 mg/m³ (long-term)
DNEL (W) dermal	6.58 mg/kg bw/day (long-term)
DNEL (G) oral	3.95 mg/kg bw/day (long-term)
DNEL (G) inhalation	6.86 mg/m³ (long-term)
DNEL (G) dermal	3.95 mg/kg bw/day (long-term)

Ecotoxicological data

Algae	EC50 (*Selenastrum capricornutum*, 72 hours): >0.86 mg/L* (OECD Guideline 201) Klimisch score: 1
Crustaceans	EC50 (*Daphnia magna*, 48 hours): >1.4 µg/L* (OECD Guideline 202) Klimisch score: 1
	NOEC (*Daphnia magna*, 21 days): >= 0.76 µg/L* (OECD Guideline 211) Klimisch score: 1

Fish	LC50 (*Pimephales promelas*, 96 hours): >984 mg/L* (OECD Guideline 203) Klimisch score: 2
	NOEC (*Oncorhynchus mykiss*, 60 days): >=0.28 mg/L* (ASTM. 1983. Proposed New Standard Practice for Conducting Fish Early Life Stages Toxicity Tests. Draft No. 7.) Klimisch score: 1
Terrestrial plants	EC50 (*Lolium perenne*, 14 days): >1400 µg/L (SEPA. 1982. Early Seedling Growth Toxicity Test, EG-13) Klimisch score: 1
Soil macroorganisms	-
PNEC (fresh water)	0.08 µg/L (Assessment factor: 10)
PNEC (marine water	0.008 µg/L (Assessment factor: 100)
PNEC (fresh water sediment)	8.28 mg/kg sediment dw (AF: 100)
PNEC (marine water sediment)	0.828 mg/kg sediment dw (AF: 1000)
PNEC (soil)	15 µg/kg soil dw (Assessment factor: 1000)

Environmental fate

Bioconcentration factor (BCF)	393 (EPA OPPTS 850.1710 (Oyster Bioconcentration Test)) Klimisch score: 1
Ready biodegradability	readily biodegradable (OECD Guideline 301 B) Klimisch score: 1
Adsorption/desorption	log Koc: 5.43, 25 °C (QSAR EPIWIN-KOWIN) (WOE) Klimisch score: 2

PBT

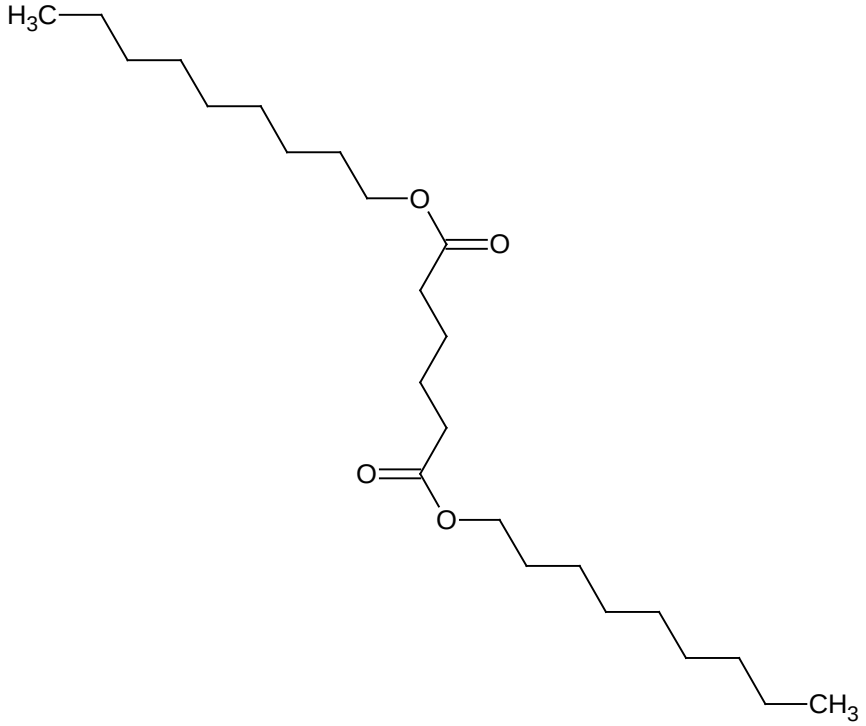
REACH registration dossier	The substance is not PBT / vPvB
QSAR	P: Neg; B: Neg; T: - ; BCF: 700
	Fish ChV (mg/L): - Half-life (Water, days): 15 Half-life (Soil, days): 30 Half-life (Sediment, days): 140 Half-life (Air, days): 0.75

QSAR bioavailability

Lipinski	Not bioavailable
Mammalian metabolism	
Microbial metabolism (observed)	ND
Microbial metabolism (simulated)	60 metabolites formed. Of these: 46 bioavailable and 14 not bioavailable. Monoesters formed.
Rat In vivo metabolism (observed)	ND
Rat In vivo metabolism(simulated)	
Rat Liver S9 metabolism (observed)	ND
Rat Liver S9 metabolism (simulated)	5 metabolites formed. Of these: 4 bioavailable and 1 not-bioavailable. Monoesters formed.
Skin metabolism	14 metabolites formed. Of these: 9 bioavailable and 5 not bioavailable. Monoesters formed.

diisononyl adipate (DINA)

Identification of substance

CAS No.	33703-08-1
EINECS No.	251-646-7
IUPAC name	diisononyl adipate
Structure	
SMILES	O=C(OCCCCCCCCC)CCCCC(=O)OCCCCCCCCC

REACH

Registration	Full
Submission	Joint Submission
Total tonnage	1,000 + tonnes per annum
Harmonised classification	Not classified
Notified classification	Not classified
REACH registration classification	Not classified
Wide dispersive end use opened/closed	Yes
Wide dispersive end use closed	Yes
Wide dispersive service life opened/closed	No
Wide dispersive service life closed	No

Physical-chemical characteristics

Molecular weight	398.63 g/mole
Vapour pressure	0.000000002 hPa, 20 °C (dynamic method) Klimisch score: 2
Henry's law constant	9.210442 Pa m³/mol, 25 °C (SRC HENRYWIN v3.10) Klimisch score: 2
Water solubility	0.0032 mg/L, 22 °C (Read-Across) Klimisch score: 2
Log K_{ow}	9.56 - 10.4, 25 °C (OECD Guideline 117) Klimisch score: 2

Toxicological data

Acute toxicity	LD50 (oral) > 5000 mg/kg bw (male/female) (OECD 401) - Klimisch score 2(key study) LD50 (dermal): no data LC50 (inhalation): 5.7 mg/L air (male/female) (OECD 403) - Klimisch score 1 (key study)
Irritation and sensitation	No skin irritation (rabbit-OECD 404) - Klimisch score 1 (key study) No eye irritation (rabbit-OECD 405) - Klimisch score 1 (key study)
Sensitation	No skin-sensitization potential (QSAR prediction) - Klimisch score 2 (WOE) No skin-sensitization potential (guinea pig maximization test - no guideline) (read-across from supporting substance: bis(2-ethylhexyl adipate) - Klimisch score 2 (WOE)
Repeated toxicity	NOAEL 200 mg/kg bw/day (male) (nominal) (28 days-OECD 407) (Read-across from bis(2-ethylhexyl) adipate CAS nr 103-23-1); LOAEL 1000 mg/kg bw/day (Increased kidney weight/histopathological changes, increased liver weight) Klimisch score 2 (key study) NOAEL 200 mg/kg bw/day (male/female) (nominal) (90 days-OECD 408) (Read-across from bis(2-ethylhexyl) adipate (CAS nr 103-23-1)) LOAEL 400 g/kg bw/day (male/female) (decreased bodyweight gain) Klimisch score 2 (key study) NOAEL 595 mg/kg bw/day (male) (nominal) (90 days-OECD 408) (Read-across from bis(2-ethylhexyl) adipate – (CAS nr 103-23-1)) LOAEL 595 mg/kg bw/day. (decreased bodyweight gain) Klimisch score 2 (key study)
Mutagenicity/genotoxicity	Negative in *in vitro* Mammalian Cell Micronucleus Test (+/- metabolic activation) (OECD 487) - Klimisch score 1 (key study) Negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (OECD 471) - Klimisch score 2 (key study) Negative in mammalian cell gene mutation assay (+/- metabolic activation) (OECD 476) - Klimisch score 1 (key study)

	Negative in *in vivo* mammalian chromosome aberration test (OECD 474) Klimisch score 2 (key study)
Endocrine	No data
Carcinogenicity	LOAEL 12000 ppm (1715 mg/kg bw/day - male/female mice) - (103 weeks OECD 451) (Read-across from bis(2-ethylhexyl) adipate – (CAS nr 103-23-1)) Di(2-ethylhexyl)adipate was carcinogenic for female mice, causing increased incidences of hepatocellular carcinomas and was probably carcinogenic for male mice, causing hepatocellular adenomas - Klimisch score 2 (key study) NOAEL 25000 ppm (600 mg/kg bw/day - male/female rats) - (103 weeks OECD 451) (Read-across from bis(2-ethylhexyl) adipate – (CAS nr 103-23-1)). Di(2-ethylhexyl)adipate was not carcinogenic (no tumour incidence) for rats at 25000 ppm in diet (considered to be equivalent to 600 mg/kg bw.) Klimisch score 2 (key study)
Reproductive and developmental toxicity	Reproductive toxicity (OECD 415-one generation) (Read-across from bis(2-ethylhexyl) adipate – (CAS nr 103-23-1)): NOAEL (parental toxicity) 170 mg/kg bw/day (nominal) LOAEL (parental toxicity) 1080 mg/kg bw/day (increased liver weight, decreased body weight gain) NOAEL (reproduction) 170 mg/kg bw/day LOAEL (reproduction) 1080 mg/kg bw/day (reduced mean pup weight gain and total litter weight) - Klimisch score 1 (key study) Developmental toxicity (OECD 414) (Read-across from bis(2-ethylhexyl) adipate – (CAS nr 103-23-1)): NOAEL (maternal toxicity) 170 mg/kg bw/day (nominal) LOAEL (maternal toxicity) 1080 mg/kg (minimal foetotoxicity (reduced bodyweight gain, feed intake) - Klimisch score 1 (key study) NOEL (developmental toxicity) 28 mg/kg bw/day LOAEL (developmental toxicity) 170 mg/kg (reduced ossification, increase in the incidence of visceral variants) - Klimisch score 1 (key study)
Toxicokinetics/Metabolism	Toxicokinetics (monkey - OECD 417): (Read-across from bis(2-ethylhexyl) adipate – (CAS nr 103-23-1)): Males showed that the majority of administered doses were recovered almost equally in urine and faeces. Trace amounts of radioactivity were present in the GI tract and blood, and minor levels were detected in tissue. Females also showed major recovery of the dose in urine and faeces. Large variations in excretion patterns were displayed by the females. Total recoveries in the four animals ranged from 89.4 to 92.6% of the dose - Klimisch score 2 (key study). Toxicokinetics (rat - OECD 417): (Read-across from bis(2-ethylhexyl) adipate – (CAS nr 103-23-1)): In males, the majority of the dose was recovered in urine (~ 74%) and faeces (~20%). Approx. 1.4% of the dose was collected in the expired air, while ~ 3.7%

	was remaining in the GI tract at 24 hr after dosing. Tissue contained ~ 2.2% of the dose and only ~ 0.2% was found in blood. Females showed similar results except for slightly lower amounts of 14C in tissue - Klimisch score 2 (key study).
	Toxicokinetics (mice - OECD 417): (Read-across from bis(2-ethylhexyl) adipate – (CAS nr 103-23-1)): Urinary elimination was rapid and extensive. About 91% of the low and mid doses (50 and 500 mg/kg) were eliminated in urine in 24 hr; only 75% after 5,000 mg/kg. Elimination in faeces was 7-8% at the low and mid doses and 4% at the high dose. The latter group showed high recovery in the GI tract. Only 0.8 to 1.2% in males and 1.5 to 3.8% in females were eliminated in the expired air. Respiratory elimination was highest in the female low dose group. Only small amounts were found in blood and tissue 24 and 48 hr after dosing. Adrenals and livers showed the highest levels at low and mid dose, especially in males. After 5,000 mg/kg, blood also contained high 14C levels; blood and liver content of the females were significantly higher than of males. At 48 hr, the skin (both sexes) and the fat (females) showed higher retention of 14C than other tissues - Klimisch score 2 (key study).
Other	Cytotoxicity: no data Hemocompability: no data
DNEL (W) oral	No data
DNEL (W) inhalation	26.5 mg/m3 (long-term)
DNEL (W) dermal	34 mg/kg bw/day (long-term)
DNEL (G) oral	1.7 mg/kg bw/day (long-term)
DNEL (G) inhalation	6.6 mg/m3 (long-term)
DNEL (G) dermal	17 mg/kg bw/day (long-term)

Ecotoxicological data

Algae	EC50 (*Scenedesmus subspicatus*, 72 hours): >100 mg/L* (OECD Guideline 201) Klimisch score: 2
Crustaceans	EC50 (*Daphnia magna*, 48 hours): >100 mg/L* (OECD Guideline 202) Klimisch score: 2
	NOEC (*Daphnia magna*, 21 days): >=0.77 mg/L* (OECD Guideline 211) (Read-across) Klimisch score: 2

Fish	LC50 (*Leuciscus idus*, 96 hours): >500 mg/L* (OECD Guideline 203) Klimisch score: 2
Terrestrial plants	-
Soil macroorganisms	LC50 (*Eisenia fetida*, 14 days): 865 mg/kg soil dw (EU Method C.8) (Read-across) Klimisch score: 2
PNEC (fresh water)	-
PNEC (marine water	-
PNEC (fresh water sediment)	-
PNEC (marine water sediment)	-
PNEC (soil)	0.865 mg/kg soil dw (Assessment factor: -)

Environmental fate

Bioconcentration factor (BCF)	27 (flow through system according to ASTM) (Read-across) Klimisch score: 2
Ready biodegradability	readily biodegradable (OECD Guideline 301 F) Klimisch score: 2
Adsorption/desorption	log Koc: 5.291 (SRC PCKOCWIN v1.66) Klimisch score: 2

PBT

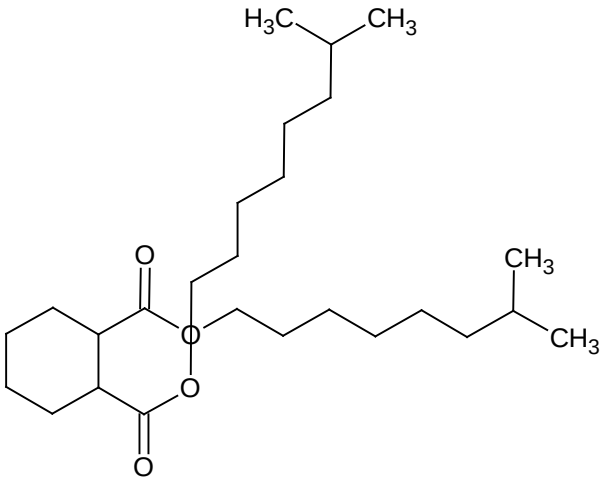
REACH registration dossier	The substance is not PBT / vPvB
QSAR	P: Neg; B: Neg; T: - BCF: 270 Fish ChV (mg/L): - Half-life (Water, days): 15 Half-life (Soil, days): 30 Half-life (Sediment, days): 140 Half-life (Air, days): 0.58

QSAR bioavailability

Lipinski	Not bioavailable
Mammalian metabolism	
Microbial metabolism (observed)	ND
Microbial metabolism (simulated)	80 metabolites formed. Of these: 64 bioavailable and 16 not bioavailable. Monoesters formed.
Rat In vivo metabolism (observed)	ND
Rat In vivo metabolism(simulated)	
Rat Liver S9 metabolism (observed)	ND
Rat Liver S9 metabolism (simulated)	15 metabolites formed. Of these: 13 bioavailable and 2 not bioavailable. Monoesters formed.
Skin metabolism	27 metabolites formed. Of these: 19 bioavailable and 8 not bioavailable. Monoesters formed.

DINCH

Identification of substance

CAS No.	166412-78-8
EINECS No.	431-890-2
IUPAC name	-
Structure	
SMILES	CC(C)CCCCCCOC(=O)C1CCCCC1C(=O)OCCCCCCC(C)C

REACH

Registration	NONS
Submission	Joint Submission
Total tonnage	Tonnage Data Confidential
Harmonised classification	Not classified
Notified classification	Not classified
REACH registration classification	Not classified
Wide dispersive end use opened/closed	No
Wide dispersive end use closed	No
Wide dispersive service life opened/closed	No
Wide dispersive service life closed	No

Physical-chemical characteristics

Molecular weight	424.67 g/mole
Vapour pressure	0.00000022 hPa, 20 °C (-)
	Klimisch score: -
Henry's law constant	7.15 Pa m^3/mol, 25°C (EPIWIN)
	Klimisch score: -
Water solubility	<0.02 mg/L, 25°C, pH 6.3 - 7.4 (-)
	Klimisch score: -
Log K_{ow}	10, 25 °C (-)

Klimisch score: -

Toxicological data*

Acute toxicity	LD50 (oral) > 5000 mg/kg bw (male/female) (OECD 423) - no Klimisch score (Key study) LD50 (dermal) > 2000 mg/kg bw (male/female) (OECD 402) - no Klimisch score (Key study) LC50 (inhalation): no data
Irritation and sensitation	Slightly skin irritation (rabbit) – (according to OECD 404) No Klimisch score (Key study) No eye irritation (rabbit) – (according to OECD 405) No Klimisch score (Key study)
Sensitation	No skin-sensitization potential (guinea pig) – (according to OECD 405) No Klimisch score (Key study)
Repeated toxicity	NOAEL 107.1-389.4 mg/kg bw/day (male-female) based on kidney weight changes (male/female) and degenerated epithelial cells (2µ-microglobulin) in the urine of males (90-day, diet – according to 408) No Klimisch score (Key study)* NOAEL 40 mg/kg bw/day (males) and 200 mg/kg bw/day (females) based on liver weight changes (both sexes) and kidney weight changes (males). Dose-related follicular cell hyperplasia and increased number of follicular adenomas were observed in the thyroid glands of male rats administered ≥ 200 mg/kg bw/day and females at 1000 mg/kg bw/day. However, thyroid effects in rats are probably secondary effects of liver enzyme induction and therefore of limited relevance to humans. (chronic toxicity according to OECD 453) - No Klimisch score (Key study)
Mutagenicity/genotoxicity	Negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (OEDC 471) - No Klimisch score (Key study) Negative in mammalian cell gene mutation assay (+/- metabolic activation) (OECD 476) - No Klimisch score (Key study) Negative in vitro mammalian chromosome aberration test (+/- metabolic activation) (OECD 473) - No Klimisch score (Key study) Negative in vivo mammalian micronucleus test (OECD 474) - No Klimisch score (Key study)
Endocrine	No significant treatment-related effects on anogenital distance were observed in any of the reproductive toxicity studies indicating no antiandrogenic effects. In general, no substance related adverse effects on normal sexual development parameters (no detailed information, data retrieved from other sources*)

	In the one-generation reproduction/developmental study - similar to OECD 414 and OECD 415), slightly decreased (significant) anogenital distance in male offspring and in the anogenital index in male and female offspring at 1000 kg/kg bw/day (highest dose level). This was considered to be spurious with no biological relevance. No effects on sexual morphology and sexual development (testes descent, vaginal opening, balanopreputial seperation) and no effect on sperm motility (F1 generation) (data retrieved from other sources*) In the two-year combined chronic toxicity/carcinogenicity study effects on thyroid was observed (increased absolute and relative thyroid weight, altered thyroid colloid, increase incidence of thyroid follicular cell adenomas at 24 months). Thyroid follicular cell proliferation and changes in TSH levels were also observed at comparable dose levels in the 90-day rat study, in a 13 week cell proliferation study, and also in female rats in the 2-generation reproduction toxicity study (data retrieved from other sources*) In the 90-day study, no peroxisome proliferative effects related to activation of the PPARα receptor were observed. No effects were observed on cyanide-insensitive palmitoyl CoA oxidase and no peroxisome accumulation was observed in any of the repeat dose oral toxicity studies. (data retrieved from other sources*) Thyroid effects in rats were evaluated to be associated with an indirect mechanism based on results from mechanistic studies. These demonstrated that, at relevant dose rates in rats, hepatic metabolic pathways involved in T4 conjugation are strongly induced, and that T3, T4 and FSH levels are perturbed in a manner consistent with an indirectly acting enzyme inducer (phenobarbital). (data retrieved from other sources*)
Carcinogenicity	NOAEL 200 mg/kg bw/day (female) NOAEL 40 mg/kg bw/day (male) (carcinogenicity study, not further described in the registration dossier - No Klimisch score (Key study)) NOAEL 1000 mg/kg bw/day (highest dose level) (OECD 453, male and female rats were administered oral doses of 40, 200, or 1000 mg/kg bw/day - no increases in malignant neoplasia up to highest dose level)
Reproductive and developmental toxicity	Reproductive toxicity (Two generations reproduction study – OECD 416): NOAEL 1000 mg/kg bw/day (parental toxicity - F0 generation-male/female) NOAEL 100 mg/kg bw/day (parental toxicity - F1 generation-male/female) LOAEL 300 mg/kg/day (hypertrophy/hyperplasia in the thyroid follicular epithelia) NOAEL 1000 mg/kg bw/day (fertility and reproduction –F0/ F1 generation-male/female) NOAEL 1000 mg/kg bw/day (foetoxicity, growth/development of offspring – F1/F2 generation) No Klimisch score (Key study)

	Reproductive toxicity (One-generation reproduction/developmental study - similar to OECD 414 and OECD 415), F0 generation females exposed (gavage) from day 6 to day 20 postpartum, sexual maturation: Slightly decreased (significant) anogenital distance in male offspring and in the anogenital index in male and female offspring at 1000 kg/kg bw/day (highest dose level). This was considered to be spurious with no biological relevance. No effects on sexual morphology and sexual development (testes descent, vaginal opening, balanopreputial seperation) and no effect on sperm motility (F1 generation). NOAEL (parental and systemic toxicity) 1000 mg/kg bw/day (highest dose level) NOAEL (foetotoxicity toxicity) 1000 mg/kg bw/day (growth/development of offspring, including sexual organ morphology and sexual maturation)* No Klimisch score (Key study).
	Developmental toxicity (rat, oral exposure by gavage): NOAEL (maternal toxicity) 1200 mg/kg bw/day NOAEL (developmental toxicity) 1200 mg/kg bw/day (OECD 414) - No Klimisch score (Key study)
	Developmental toxicity (rabbit, oral exposure via feed): NOAEL (maternal toxicity) 1000 mg/kg bw/day NOAEL (developmental toxicity) 1000 mg/kg bw/day (OECD 414) - No Klimisch score (Key study)
Toxicokinetics/Metabolism	3 studies indicated in the registration dossier but public data not available. DINCH is rapidly absorbed after oral administration and readily eliminated. After 48 hours more than 90% is excreted via urine and mainly via faeces. Bile and urine contained up to 50% of the administered dose. No information was found with respect to dermal absorption, but no systemic toxicity has been observed in acute dermal studies, indicating low absorption. The main metabolites of DINCH in rats is the monoisononyl ester (as glucuronide conjugate), which is the most abundant metabolite in bile, and the (unconjugated) urinary metabolites cyclohexane-1, 2-dicarboxylic acid and monohydroxyisononyl ester*
Other	Blood bags formulated with DINCH: No negative effects on storage parameters of erythrocyte parameters (data supplied from manufacturer)
DNEL (W) oral	No data
DNEL (W) inhalation	35 mg/m^3 (long-term)
DNEL (W) dermal	41 mg/kg bw/day (long-term)
DNEL (G) oral	2 mg/kg bw/day (long-term)
DNEL (G) inhalation	21 mg/m3 (long-term)

DNEL (G) dermal	25 mg/kg bw/day (long-term)

Ecotoxicological data

Algae	EC50 (*Scenedesmus subspicatus*, 72 hours): >100 mg/L* (-) Klimisch score: -
Crustaceans	EC50 (*Daphnia magna*, 48 hours): >100 mg/L* Klimisch score: -
	NOEC (*Daphnia magna*, 21 days): >=0.021 mg/L* Klimisch score: -
Fish	LC50 (*Brachydanio rerio*, 96 hours): >100 mg/L* Klimisch score: -
	-
Terrestrial plants	EC50 (*Avena sativa/Brassica napus/Vicia sativa*, 20 days): >1000 mg/kg soil dw Klimisch score: -
Soil macroorganisms	LC50 (*Eisenia fetida*, 14 days): >1000 mg/kg Klimisch score: -
PNEC (fresh water)	-
PNEC (marine water	-
PNEC (fresh water sediment)	-
PNEC (marine water sediment)	-
PNEC (soil)	10 mg/kg soil dw (Assessment factor: -)

Environmental fate

Bioconcentration factor (BCF)	189.3 (-) Klimisch score: -
Ready biodegradability	inherently biodegradable (no conclusion in dossier) (-) Klimisch score: -
Adsorption/desorption	log Koc: 6.59 (-) Klimisch score: -

PBT

REACH registration dossier	-
QSAR	P: Pos; B: Neg; T: -; BCF: 3.2 Fish ChV (mg/L): - Half-life (Water, days): 38 Half-life (Soil, days): 75 Half-life (Sediment, days): 340 Half-life (Air, days): 0.58

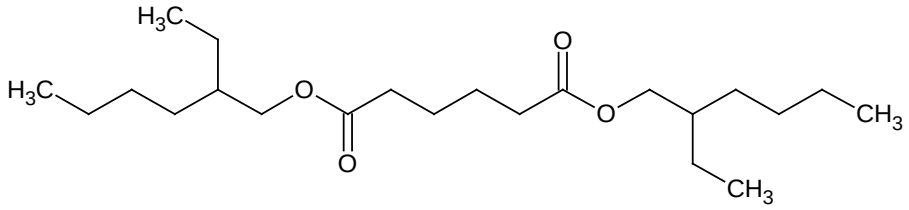
QSAR bioavailability

Lipinski	Not bioavailable
Mammalian metabolism	Not bioavailable
Microbial metabolism (observed)	
Microbial metabolism (simulated)	ND
Rat In vivo metabolism (observed)	92 metabolites formed. Of these: 66 bioavailable and 26 not bioavailable. Monoesters formed.
Rat In vivo metabolism(simulated)	ND
Rat Liver S9 metabolism (observed)	
Rat Liver S9 metabolism (simulated)	ND
Skin metabolism	7 metabolites formed. Of these: 5 bioavailable and 2 not bioavailable. Monoesters formed.

*Testing data from the REACH registration dossier was limited. Further information was extracted from the reference "Analysis of Alternatives (non-confidential report), Hazard and risk evaluation of DEHP alternatives prepared on behalf of the DEHP authorization task force (ATF), June 2013 – ARKEMA, France" , the public report from the Australian Authorities NICNAS, February 2012 and the GreenScreen assessment from Toxservices, 2012.

DOA (Bis(2-Ethylhexyl) Adipate)

Identification of substance

CAS No.	103-23-1
EINECS No.	-
IUPAC name	-
Structure	
SMILES	O=C(OCC(CCCC)CC)CCCCC(=O)OCC(CCCC)CC

REACH

Registration	Full
Submission	Joint Submission
Total tonnage	10,000 - 100,000 tonnes per annum
Harmonised classification	Not classified
Notified classification	Not classified
REACH registration classification	Not classified
Wide dispersive end use opened/closed	
Wide dispersive end use closed	
Wide dispersive service life opened/closed	
Wide dispersive service life closed	

Physical-chemical characteristics

Molecular weight	370.58 g/mole
Vapour pressure	ca. 0.0000003 hPa , 20 °C (Calculated value in accordance with generally accepted standard methods) Klimisch score: 2
Henry's law constant	5.06 Pa m^3/mol, 25°C (SRC HENRYWIN v3.10) Klimisch score: 2
Water solubility	0.0032 mg/L, 22 °C (-) Klimisch score: 2
Log K_{ow}	8.94, 25 °C (OECD 117) Klimisch score: 2

Toxicological data

Acute toxicity	LD50 (oral) 45000 mg/kg bw (male), 24600 mg/kg bw (female) (OECD 401) Klimisch score 2 (key study) LD50 (dermal): No data LC50 (inhalation) > 5.7 mg/L air (OECD 403)

	Klimisch score 1 (key study)
Irritation and sensitation	No skin irritation (rabbit-OECD 404) - Klimisch score 1 (key study) No eye irritation (rabbit-OECD 405) - Klimisch score 1 (key study)
Sensitation	No skin-sensitization - Klimisch score 2 (key study)
Repeated toxicity	NOAEL 200 mg/kg bw/day (male/female) (nominal) (28 days OECD 407) - Klimisch score 2 (key study) NOAEL 600 mg/kg bw/day (male/female) (nominal) (103 weeks OECD 451) - Klimisch score 2 (key study)
Mutagenicity/genotoxicity	Negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (OECD Guideline 471) - Klimisch score 2 (key study) Negative in mammalian cell gene mutation assay (+/- metabolic activation) (OECD Guideline 476) - Klimisch score 2 (key study) Negative in vitro mammalian chromosome aberration test (+/- metabolic activation) - Klimisch score 2 (key study) Negative in vivo micronucleus assay (mice) - Klimisch score 2 (key study)
Endocrine	No specific data on this endpoint was included in the REACH registration dossier. In relation to a possible endocrine activity, the following is referenced from secondary source: “some studies reported the lack of an antiandrogenic effect or estrogenic activity. No estrogenic activity was observed in transgenic mice, expressing an oestrogen receptor (ER) - mediated luciferase (luc) reporter gene system. DEHA affected thyroid hormone function in rats (TH-dependent rat pituitary GH3 cell proliferation, T-screen), but not the oestrogen receptor function in human breast MVLN cells”. Further in a developmental toxicity test using dose levels of up to 800 mg/kg bw/day, no effect were noted with respect to reproductive hormones, sperm quality, weight and histopathology of male reproductive organs*
Carcinogenicity	LOAEL 1715 mg/kg bw/day (nominal) (Carcinogenicity- male/female mice) - (103 weeks - OECD 451) Di (2-ethylhexyl)adipate was carcinogenic for female mice, causing increased incidences of hepatocellular carcinomas, and was probably carcinogenic for male mice, causing hepatocellular adenomas. Klimisch score 2 (key study) NOAEL 1250 mg/kg bw/day (nominal) (Carcinogenicity- male/female rats) - (103 weeks - OECD 451) Klimisch score 2 (key study) A comparative study for peroxisome proliferators was conducted with DEHA. Rats and mice were fed up to 2% DEHA for 30days. Peroxisome proliferating effects were detected.

	Klimisch score 2 (supporting study)
Reproductive and developmental toxicity	Reproductive toxicity (one generation - OECD 415): NOAEL 170 mg/kg bw/day (nominal) (F0 generation-male/female) LOAEL 1080 mg/kg bw/day (F0 generation-male/female) (increased absolute liver weights, and reduced body weight gain) NOAEL 170 mg/kg bw/day (nominal) (F1 generation-male/female) LOAEL 1080 mg/kg bw/day) (F1 generation-male/female) (reduced mean pup weight gain and total litter weight for offspring) Klimisch score 1 (key study) Reproductive toxicity (one generation - OECD 415): Combined Repeated Dose and Reproduction /Developmental Toxicity Screening Test using dose levels of 40, 200, 1000 mg/kg/day. The treatment period was described as being at least 28 days. NOAEL 200 mg/kg bw/day (nominal) LOAEL 1000 mg/kg bw/day (Increase of follicle atresia in ovaries, and abnormal estrous cycling at 1000 mg/kg). Klimisch score 2 (supporting study) Developmental toxicity (OECD 414): NOAEL (maternal toxicity) 170 mg/kg bw/day (body weight reduction) NOEL (foetotoxicity) 28 mg/kg bw/day (reduced ossification and increased incidence of visceral variants) Klimisch score 1 (key study)
Toxicokinetics/Metabolism	Toxicokinetics (rat - OECD 417): In males, the majority of the dose was recovered in urine (~ 74%) and faeces (~20%). Approx. 1.4% of the dose was collected in the expired air, while ~ 3.7% was remaining in the GI tract at 24 hr after dosing. Tissue contained ~ 2.2% of the dose and only ~ 0.2% was found in blood. Females showed similar results except for slightly lower amounts of 14C in tissue. Klimisch score 1 (key study) Toxicokinetics (mice - OECD 417): Urinary elimination was rapid and extensive. About 91% of the low and mid doses (50 and 500 mg/kg) were eliminated in urine in 24 hr; only 75% after 5,000 mg/kg. Elimination in faeces was 7-8% at the low and mid doses and 4% at the high dose. The latter group showed high recovery in the GI tract. Only 0.8 to 1.2% in males and 1.5 to 3.8% in females were eliminated in the expired air. Respiratory elimination was highest in the female low dose group. Only small amounts were found in blood and tissue 24 and 48 hr after dosing. Adrenals and livers showed the highest levels at low and mid dose, especially in males. After 5,000 mg/kg, blood also contained high 14C levels; blood and liver content of the females were significantly higher than of males. At 48 hr, the skin (both sexes) and the fat (females) showed higher retention of 14C than other tissues. Klimisch score 1 (key study) Toxicokinetics (monkey - OECD 417): Males showed that the majority of administered doses were recovered almost

	equally in urine and faeces. Trace amounts of radioactivity were present in the GI tract and blood, and minor levels were detected in tissue. Females also showed major recovery of the dose in urine and faeces. Large variations in excretion patterns were displayed by the females. Total recoveries in the four animals ranged from 89.4 to 92.6% of the dose. Klimisch score 1 (key study)
Other	Cytotoxicity: no data Hemocompability: no data
DNEL (W) oral	No data
DNEL (W) inhalation	17.8 mg/m³ (long-term)
DNEL (W) dermal	25.5 mg/kg bw/day (long-term)
DNEL (G) oral	1.3 mg/kg bw/day (long-term)
DNEL (G) inhalation	4.4 mg/m³ (long-term)
DNEL (G) dermal	13 mg/kg bw/day (long-term)

Ecotoxicological data

Algae	EC50 (*Scenedesmus subspicatus*, 72 hours): >500 mg/L (DIN 38412, part 9) Klimisch score: 2
Crustaceans	EC50 (*Daphnia magna*, 48 hours): > 500 mg/L (OECD Guideline 202) Klimisch score: 2
	NOEC (*Daphnia magna*, 21 days): >=0.77 mg/L (OECD Guideline 211) Klimisch score: 2
Fish	LC0 (*Oncorhynchus mykiss*, 96 hours): > 0.78 mg/L (EPA-66013-75-009: Methods for acute toxicity tests with fish, macro invertebrates, and amphibians) Klimisch score: 2
	-
Terrestrial plants	-
Soil macroorganisms	LC50 (*Eisenia fetida*, 7 days): >1000 mg/kg soil dw

	(EU Method C.8) Klimisch score: 2
PNEC (fresh water)	0.0032 mg/L (Assessment factor: -)
PNEC (marine water	0.0032 mg/L (Assessment factor: -)
PNEC (fresh water sediment)	15.6 mg/kg sediment dw
PNEC (marine water sediment)	-
PNEC (soil)	0.865 mg/kg soil dw (Assessment factor: 1000)

Environmental fate

Bioconcentration factor (BCF)	27 (flow through system according to ASTM) Klimisch score: 2
Ready biodegradability	readily biodegradable Klimisch score: 2
Adsorption/desorption	log Koc: 4.687 (SRC PCKOCWIN v Klimisch score: 2

PBT

REACH registration dossier	The substance is not PBT / vPvB
QSAR	P: Neg; B: Neg; T: - ; BCF: 960 Fish ChV (mg/L): - Half-life (Water, days): 8.7 Half-life (Soil, days): 17 Half-life (Sediment, days): 78 Half-life (Air, days): 0.62

QSAR bioavailability

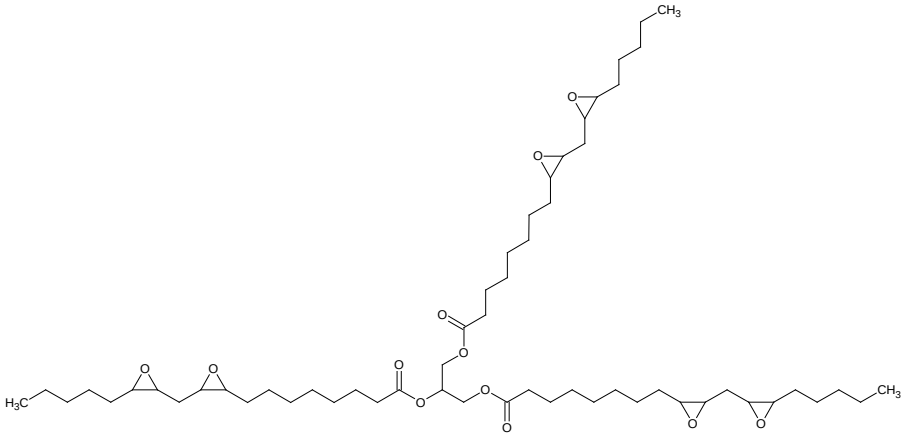
Lipinski	Not bioavailable
Mammalian metabolism	
Microbial metabolism (observed)	5 metabolites formed. Of these: 5 bioavailable and 0 not bioavailable. Monoesters formed.
Microbial metabolism (simulated)	53 metabolites formed. Of these: 43 bioavailable and 10 not bioavailable. Monoesters formed.
Rat In vivo metabolism (observed)	2 metabolites formed. Of these: 2 bioavailable and 0 not bioavailable. Monoesters formed.
Rat In vivo metabolism(simulated)	
Rat Liver S9 metabolism	2 metabolites formed. Of these: 2 bioavailable and 0 not bioavailable.

(observed)	Monoesters formed.
Rat Liver S9 metabolism	7 metabolites formed. Of these: 7 bioavailable and 0 not bioavailable.
(simulated)	Monoesters formed.
Skin metabolism	14 metabolites formed. Of these: 10 bioavailable and 4 not bioavailable.
	Monoesters formed.

*Testing data from the REACH registration dossier was limited. Further information was extracted from the reference "Analysis of Alternatives (non-confidential report), Hazard and risk evaluation of DEHP alternatives prepared on behalf of the DEHP authorization task force (ATF), June 2013 – ARKEMA, France".

ESBO (Epoxidised soybean oil)

Identification of substance

CAS No.	8013-07-8
EINECS No.	-
IUPAC name	-
Structure	
SMILES	C(=O)(CCCCCCCC1C(CC2C(CCCCC)O2)O1)OC(COC(=O)CCCCCCCC1C(CC2C(CCCCC)O2)O1)COC(=O)CCCCCCCC1C(CC2C(CCCCC)O2)O1

REACH

Registration	Full
Submission	Joint Submission
Total tonnage	10,000 - 100,000 tonnes per annum
Harmonised classification	Not classified
Notified classification	Not classified
REACH registration classification	Not classified
Wide dispersive end use opened/closed	
Wide dispersive end use closed	
Wide dispersive service life opened/closed	
Wide dispersive service life closed	

Physical-chemical characteristics

Molecular weight	940-950 g/mole
Vapour pressure	8.4 x 10-8 Pa at 25°C (using a vapour pressure balance) Klimisch score: 1 (key study)
Henry's law constant	No data
Water solubility	< 0.02 µg/L at 20°C (calculated using Advanced Chemistry Development (ACD/Labs) Software V9.04 ((C) 1994-2010 ACD/Labs) < 0.05 mg/L at 20°C (OECD Guideline 105) < 0.00136 g/L at 20°C (OECD Guideline 105) Klimisch score: 2; 2; 1 (key studies)

Log K_{ow}	> 6.2 (OECD Guideline 117) Klimisch score: 1 (key study)

Toxicological data

Acute toxicity	LD50 (oral) > 5000 mg/kg bw (OECD 401) Klimisch score 2 (key study) LD50 (dermal) >20 mL/kg bw (similar to OECD 402) Klimisch score 2 (key study) LD50 (inhalation): No data
Irritation and sensitation	Slightly irritating to the skin (rabbit-similar to OECD 404) Klimisch score 1 (key study) Slightly irritating to the eye (rabbit-OCED 405) Klimisch score 1 (key study)
Sensitation	Not sensitizing (guinea pig-OECD 406) Klimisch score 2 (key study)
Repeated toxicity	NOEL 1000 mg/kg bw/day (2.5%) (highest dose tested) (male) and 1400 mg/kg bw/day (2.5%) (highest dose tested) (female) (104 weeks in diet- similar to OECD Guideline 453) - Klimisch score 1-2 (key study) NOAEL 1000 mg/kg bw/day (increased liver weight) (male/female) NOEL 100 mg/kg bw/day (male/female) (90 days - OECD Guideline 422) - Klimisch score 1 (key study)
Mutagenicity/genotoxicity	Negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (OECD Guideline 471) - Klimisch score 2 (key study) Negative in mammalian cell gene mutation assay (+/- metabolic activation) (OECD Guideline 476) - Klimisch score 1 (key study) Negative in vitro mammalian chromosome aberration test (+/- metabolic activation) (OECD Guideline 473) - Klimisch score 1 (key study)
Endocrine	No data
Carcinogenicity	NOEL 1000 mg/kg bw/day (2.5%) (highest dose tested) (male) and 1400 mg/kg bw/day (2.5%) (highest dose tested) (female) (104 weeks in diet- similar to OECD Guideline 453) - Klimisch score 1-2 (key study)
Reproductive and developmental toxicity	Reproductive toxicity (one-generation - OECD 415): NOEC > 1000 mg/kg bw/day (highest dose tested) Klimisch score 2 (key study) Developmental toxicity (OECD 414): NOEL (maternal toxicity) 1000 mg/kg bw/day (highest dose tested) NOEL (developmental toxicity) 1000 mg/kg bw/day (highest dose tested) Klimisch score 2 (key study)

Toxicokinetics/Metabolism	No data
Other	Cytotoxicity: no data Hemocompability: no data
DNEL (W) oral	No data
DNEL (W) inhalation	11.9 mg/m³ (long-term); 70 mg/m³ (short term)
DNEL (W) dermal	1.7 mg/kg bw/day (long term); 10 mg/kg bw/day (short term)
DNEL (G) oral	0.8 mg/kg bw/day (long term); 5 mg/kg bw/day (short term)
DNEL (G) inhalation	10 mg/kg bw/day (long term); 17.5 mg/m³ (short term)
DNEL (G) dermal	0.8 mg/kg bw/day (long term); 5 mg/kg bw/day (short term)

Ecotoxicological data

Algae	EC50 (*Scenedesmus subspicatus*, 72 hours): 8 mg/L (Directive 87/302/EEC, part C, p. 89 "Algal inhibition test") Klimisch score:
Crustaceans	EC50 (*DM*, 24 hours): >100 mg/L (OECD Guideline 202) Klimisch score:
	-
Fish	LC50 (*Leuciscus idus*, 48 hour): 900 mg/L (-) Klimisch score:
	-
Terrestrial plants	-
Soil macroorganisms	-
PNEC (fresh water)	-
PNEC (marine water	-
PNEC (fresh water	-

sediment)	
PNEC (marine water sediment)	-
PNEC (soil)	- (Assessment factor: -)

Environmental fate

Bioconcentration factor (BCF)	-
Ready biodegradability	-
Adsorption/desorption	-

PBT

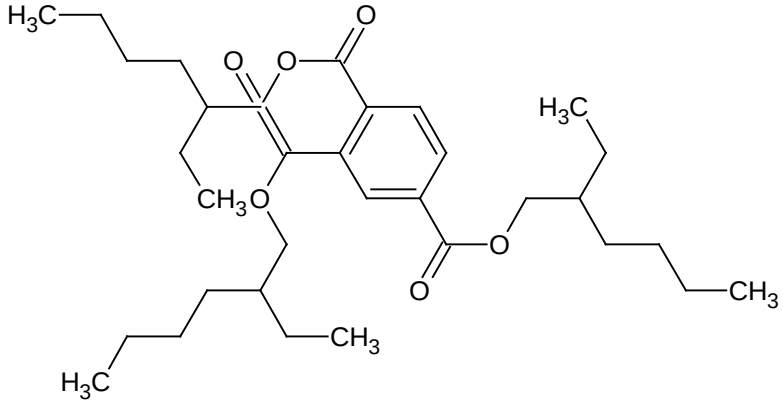
REACH registration dossier	-
QSAR	P: Pos; B: Neg; T: - ; BCF: 3.2 Fish ChV (mg/L): - Half-life (Water, days): 38 Half-life (Soil, days): 75 Half-life (Sediment, days): 340 Half-life (Air, days): 0.27

QSAR bioavailability

Lipinski	Not bioavailable
Mammalian metabolism	
Microbial metabolism (observed)	ND
Microbial metabolism (simulated)	225 metabolites formed. Of these: 150 bioavailable and 75 not bioavailable. Monoesters formed.
Rat In vivo metabolism (observed)	ND
Rat In vivo metabolism(simulated)	
Rat Liver S9 metabolism (observed)	ND
Rat Liver S9 metabolism (simulated)	13 metabolites formed. Of these: 0 bioavailable and 13 not bioavailable. Monoesters formed.
Skin metabolism	ND

TOTM/TEHTM (Trioctyl trimellitate/Tri-(2-ethylhexyl)- trimellitate)

Identification of substance

CAS No.	3319-31-1
EINECS No.	222-020-0
IUPAC name	tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate
Structure	
SMILES	O=C(OCC(CCCC)CC)c(ccc(c1C(=O)OCC(CCCC)CC)C(=O)OCC(CCCC)CC)c1

REACH

Registration	Full
Submission	Joint Submission
Total tonnage	10,000 - 100,000 tonnes per annum
Harmonised classification	No classification
Notified classification	No classification
REACH registration classification	No classification
Wide dispersive end use opened/closed	
Wide dispersive end use closed	
Wide dispersive service life opened/closed	
Wide dispersive service life closed	

Physical-chemical characteristics

Molecular weight	g/mole
Vapour pressure	ca. 0.000000068 Pa, 25 °C (EU Method A.4 (Vapour Pressure))
	Klimisch score: 1
Henry's law constant	0.0506 Pa m^3/mol, 25 °C (HENRYWIN (v3.20)) (QSAR)
	Klimisch score: 2
Water solubility	3.06 µg/L, 25 °C, pH 4.81 (OECD Guideline 105)
	Klimisch score: 1
Log K_{ow}	8, 25 °C, pH 4.81 (OECD Guideline 123)
	Klimisch score: 1

Toxicological data

Acute toxicity	LD50 (oral) > 2000 mg/kg bw) (OECD 401) - Klimisch score 2 (key study) LD50 (dermal) > 2mL/kg bw - Klimisch score 2 (key study) LC50 (inhalation) > 2600 mg/m3 air (OECD 403) - Klimisch score 2 (key study)
Irritation and sensitation	Slightly skin irritation (rabbit) - Klimisch score 2 (key study) No eye irritation (rabbit) - Klimisch score 2 (key study)
Sensitation	No skin sensitization (guinea pigs-OECD 406) - Klimisch score 2 (key study)
Repeated toxicity	NOAEL 225 mg/kg bw/day LOAEL 1000 mg/kg bw/day (blood chemistry changes, liver weight increase, pathology changes in liver and spleen) (The 90 day feeding study using dose levels of 50, 225 and 1000 mg/kg bw day included additionally an analysis of spermatogenic cycling (histology of testis, staging according to Creasy 2002) and oestrous cycle (last 2 weeks of treatment, vaginal smear). No adverse effects were observed on these parameters and on the histology of the reproductive organs) (90 day, rat (Sprague-Dawley)- OECD 408) - Klimisch score 1 (key study) NOAEL 184 mg/kg bw/day (0.2%) LOAEL 650 mg/kg bw/day (0.67%) (liver enlargement, increases in palmitoyl-CoA oxidation and the activities of catalase and carnitine acetyltransferase and the induction of slight peroxisome proliferation - same spectrum of morphological and biochemical changes to the rat liver as DEHP although TOTM was much less potent) (28 day, rat - no info on guideline) - Klimisch score 2 (supplementary study)
Mutagenicity/genotoxicity	Negative in Bacterial Reverse Mutation Assay (+/- metabolic activation) (OECD 471) - Klimisch score 1 (key study) Negative in mammalian cell gene mutation assay (+/- metabolic activation) (OECD 476) - Klimisch score 1 (key study) Negative in *in vitro* mammalian chromosome aberration test (+/- metabolic activation) (OECD 473) - Klimisch score 1 (key study)
Endocrine	No significant repressive effect of TOTM on the expression of genes in pathways known to be involved in steroidogenesis and testicular mal-development (TMD) in the rat (e.g. steroidogenesis, cholesterol metabolism and transport and guvernacular ligament development). Positive control substances (MEHP and DEHP) caused a repression of genes involved in testes development and cholesterol and testosterone biosynthesis (male rats (Han Wistar) exposed in utero from gestation days 12 to 19 by oral gavage of 500 mg/kg, transcriptional profiling analysis of RNA extracted from neonatal testes - no guideline) - Klimisch score 1 (supplementary study)
Carcinogenicity	Negative based on QSAR prediction - Klimisch score 2 (supplementary study)
Reproductive and	Reproductive toxicity (rat (Crj:CD:SD) - OECD 421):

developmental toxicity	NOAEL (parental toxicity) 1000 mg/kg bw/day NOAEL (fertility) 100 mg/kg bw/day (male) LOAEL (fertility) 300 mg/kg bw/day (male) (Reduced numbers of spermatocytes and spermatids. However no effects with respect to spermatogenic cyclus and testes histopathology was noted in the 90-day study described in the above section using another rat strain (Sprague-Dawley) up to a dose level of 1000 mg/kg bw/day) NOAEL (developmental toxicity) 1000 mg/kg bw/day Klimisch score 2 (key study) Developmental toxicity (rat - OECD 414): NOAEL (maternal toxicity) 1050 mg/kg bw/day NOAEL (developmental toxicity) 1050 mg/kg bw/day NOAEL (post-natal development) 500 mg/kg bw/day LOAEL (post-natal development) 1050 mg/kg bw/day (slight increase in retained areolar region in males postnatal day 13, no longer present at postnatal day 18, slightly higher increase in displaced testes compared to controls although the observed incidence was within the range of historical control data). No effects upon sexual maturation or development of the reproductive tract in male or female offspring that were attributed to treatment. Klimisch score 1 (key study)
Toxicokinetics/Metabolism	Toxicokinetics (rat - OECD 417): TOTM is only partially hydrolysed in the gastro-intestinal tract to 2-ethylhexanol and the corresponding di-ester and, following further hydrolysis, the mono-ester. Only 2-ethylhexanol and a single isomer of mono-(2-ethylhexyl)trimellitate appear to be absorbed. Following absorption, 2-ethylhexanol was extensively metabolised with metabolites eliminated in the urine and as expired $^{14}CO2$. There was no evident metabolism of mono-(2-ethylhexyl)trimellitate, this being eliminated unchanged. Klimisch score 1 (key study) Low dermal absorption based on QSAR analyses. Klimisch score 2 (key study)
Other	Cytotoxicity: No data Hemocompability: No data
DNEL (W) oral	No data
DNEL (W) inhalation	3.97 mg/m3 (long-term)
DNEL (W) dermal	22.5 mg/kg bw/day (long-term)
DNEL (G) oral	1.13 mg/kg bw/day (long-term)
DNEL (G) inhalation	0.98 mg/m^3 (long-term)
DNEL (G) dermal	11.25 mg/kg bw/day (long-term)

Ecotoxicological data

Algae	EC50 (*Selenastrum capricornutum*, 72 hours): >100 mg/L (OECD Guideline 201) Klimisch score: 2
Crustaceans	EC50 (*Daphnia magna*, 48 hours): >180 mg/L (OECD Guideline 202) Klimisch score: 2
	NOEC (*Daphnia magna*, 21 days): 55.6 mg/L (OECD Guideline 211) Klimisch score: 2
Fish	LC50 (*Oryzias latipes*, 96 hours): >100 mg/L (OECD Guideline 203) Klimisch score: 2
	NOEC (*Oryzias latipes*, 14 days): >75 mg/L (OECD Guideline 204) Klimisch score: 2
Terrestrial plants	LC50 (*Triticum aestivum*, 18 days): >100 mg/kg soil dw (OECD guideline 208) (Read-across) Klimisch score: 2
Soil macroorganisms	LC10 (*Eisenia fetida*, 14 days): >1000 mg/kg soil dw (EU Method C.8) (Read-across) Klimisch score: 2
PNEC (fresh water)	60 ng/L (Assessment factor: 50)
PNEC (marine water	6 ng/L (Assessment factor: 500)
PNEC (fresh water sediment)	7.4 mg/kg sediment dw
PNEC (marine water sediment)	0.74 mg/kg sediment dw
PNEC (soil)	0.095 mg/kg soil dw (Assessment factor: 1000)

Environmental fate

Bioconcentration factor (BCF)	2.7 (OECD Guideline 305 C) Klimisch score: 2
Ready biodegradability	inherently biodegradable, fulfilling specific criteria Klimisch score: 1
Adsorption/desorption	log Koc: 22.96, 20 °C (OECD Guideline 121) Klimisch score: 1

PBT

REACH registration dossier	Further information relevant for the PBT assessment is necessary
QSAR	P: Neg; B: Neg; T: -; BCF: 19 Fish ChV (mg/L): - Half-life (Water, days): 8.7 Half-life (Soil, days): 17 Half-life (Sediment, days): 78 Half-life (Air, days): 0.5

QSAR bioavailability

Lipinski	Not bioavailable
Mammalian metabolism	
Microbial metabolism (observed)	ND
Microbial metabolism (simulated)	110 metabolites formed. Of these: 63 bioavailable and 47 not bioavailable. Monoesters formed.
Rat In vivo metabolism (observed)	2 metabolites formed. Of these: 1 bioavailable and 1 not-bioavailable. Monoesters formed.
Rat In vivo metabolism(simulated)	
Rat Liver S9 metabolism (observed)	ND
Rat Liver S9 metabolism (simulated)	10 metabolites formed. Of these: 7 bioavailable and 3 not bioavailable. Monoesters formed.
Skin metabolism	40 metabolites formed. Of these: 5 bioavailable and 35 not bioavailable. Monoesters formed.

Alternatives to classified phthalates in medical devices

Overall, the report identified 10 potential alternatives to DEHP in medical devices. The alternatives have been studied for their inherent environmental and health properties. Most of the considered alternatives show a better toxicological profile than DEHP, and are thus preferable to DEHP. However, data are lacking for a few of the alternatives, before a toxicological assessment can be carried out.

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