Environmental Project No. 590 2001
Miljøprojekt

Environmental and Health Assesment of Alternatives to Phthalates and to flexible PVC

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Foreword

In June 1999 the Danish strategy and action plan to reduce PVC and phthalate plasticisers in flexible plastics was published. The aim of the plan is a 50% reduction in the use. The Danish EPA has initiated a range of projects on issues related to substitution of PVC and phthalate plasticisers following publishing

The present project is a forecast of the use, exposure, and possible health and environmental effects of several alternative plasticisers and of two materials suggested for substitution of flexible PVC.

The project report comprises a main summarising section and an appendix section containing detailed data sheets and other information on each substance and material evaluated.

The project was commenced in January 2000 and completed in December 2000. The contained information reflects the data available to the project team at that time. An advisory group has followed the project during the preparation. The members were:

Lea Frimann Hansen – Danish EPA (chairman)
Pernille Andersen - The Graphic Association of Denmark (GA)
Annette Harbo - The Danish Paintmakers Association
Ole Ladefoged – The Danish Veterinary and Food Administration
Pernille Thomsen – The Danish Plastics Federation, Denmark (to 31.07.00)
Lars Blom – The Danish Plastics Federation, Denmark (from 01.08.00)
Annette Tølløse – The Danish Medicines Agency
Bent Horn Andersen - National Working Environment Authority
Aage Feddersen - Federation of Danish Textile and Clothing (FDTC)
Frank Stuer-Lauridsen - COWI

The project was carried out at COWI Consulting Engineers & Planners by a team of consultants consisting of Frank Stuer-Lauridsen (project manager), Sonja Mikkelsen, Sven Havelund, Morten Birkved and Lisbet P. Hansen.

1 Summary

Phthalates and PVC

Phthalates are a group of plasticisers, which among others is used for manufacturing of soft PVC. In recent years laboratory experiments have shown that some of the phthalates may have toxicological and ecotoxicological effects, e.g. impaired capacity for reproduction in laboratory animals Effects are seen at levels, which give rise to concern in relation to exposure of man and environment. Five phthalates are under risk assessment in the EU. In Denmark a plan for 50% reduction over the next 10 years has been adopted. Other countries like Sweden and Germany have a similar objective. It is therefore to be expected that the need for alternatives to the existing plasticisers will grow in the near future. In this report a range of alternatives to phthalates and flexible PVC has been assessed with respect to their inherent properties and potential risk for humans and the environment.

Evaluated substances and materials

The Danish Environmental Protection Agency (DEPA) had in advance selected five substances and in concert with the industry another six substances were selected as examples for the remaining groups of alternative plasticisers. Also two polymeric materials were selected as alternatives to flexible PVC. A data search in readily available databases was performed at first. On this basis preliminary data sheets were produced for the physico-chemical, health and environmental properties of the substances. A possible substitution pattern expected for phthalates in Denmark was developed based on information from the Danish Product Register, suppliers and the industry.

<u>Substances</u>

- Diethylhexyl adipate
- O-acetyltributyl citrate
- Di(2-ethylhexyl) phosphate
- Tri(2-ethylhexyl) phosphate
- Tri-2-ethylhexyl trimellitate

<u>Groups of substances</u>

- Alkylsulphonic acid esters
- Butane esters
- Polyester
- Epoxyester and epoxydized oils
- Benzoate
- Sebacates

<u>Materials</u>

- Polyurethane
- Polyethylene

Exposure, health and environmental properties

Key data for the assessment of toxicological effects in man and the environment were identified. For these data additional information was obtained in the original literature and presented in more detail in the main report.

Screening of health and environmental effects are based on inherent properties. The risk to man and environment is illustrated through two possible exposure scenarios: one scenario based on an expected substitution pattern and another scenario based on substitution of the total consumption of phthalates for a particular use with the actual plasticiser. The estimation and comparison was carried out according to principles of the EU Technical Guidance Document. Exposures were determined using the EASE and EUSES models, which were supplied with substance data and amounts for

the chosen exposure conditions. The physical dimensions of the regional scenario were set at values representative for Denmark.

Table 1.1
The registered use of the selected substances as plasticisers in the selected product groups. Data obtained from the Danish Product Register. The polyester plasticiser (polyadipate) was not included due to lack of CAS no.

CAS No.	Name (synonym may used in the Danish Product Register)	Fillers	Paint and lacquers	Adhesives	Printing inks	Plastic in Concrete	Rubber products	PVC packaging
103-23-1	Di(ethylhexyl) adipate	•	•	•		•	•	
77-90-7	O-acetyl tributyl citrate				•	•		
298-07-7	Di(2-ethylhexyl) phosphate							
78-42-2	Tri(2-ethylhexyl) phosphate	•	•	•		•		
3319-31-1	Tri-2-ethylhexyltrimellitate *							
88-19-7	O-toluene sulfonamide *							
6846-50-0	Butane ester (2,2,4-trimethyl 1,3-pentanedioldiisobutyrate)	•	•		•	•		•
8013-07-8	Epoxidised soybean oil	•	•	•	•			•
27138-31-4	Dipropylene glycol dibenzoate				•			
122-62-3	Dioctyl sebacate			•				

* Not found in the Product Register.

Migration and volatility

The key parameters with respect to release of plasticisers under polymer production and consumer use, are potential for evaporation and migration out of the PVC polymer. Some data exist for volatility, but only few data have been identified on migration potential for the substitutes.

Assessment of polymer materials

The assessment principles in the EU Technical Guidance Document are only applicable for substances. The polyadipate plasticiser and the two materials are assessed based on their monomers and oligomers as well as on general properties of polymers. Based on the obtained data it is estimated that the polyadipate and the two materials will have no immediate effects in the consumer use situation or in the environment.

Assessment of substances

A comparative assessment of the substances is difficult, as only few and often different parameters are available for some of the substances. Quantitative ranking is not a possibility with the available data set presented for the substances. In the following two tables (Table 1.2 and Table 1.3) a summation of the inherent hazardous properties and the potential risks from use of the suggested alternatives are presented.

The selected key properties (inherent properties) with rspect to humans are those effects, which manifest themselves immediately after exposure and chronic effects, which may arise from a single or repeated exposure. For these properties it is evaluated whether thay fulfil the criteria for classification according to the EU regulations. Key properties with respect to the en-

vironment are persistence, bioaccumulation and aquatic toxicity. For those parameters it is also evaluated whether they fulfil the EU classification criteria for the aquatic environment.

The assessment of the risks to man and environment in relation to the investigated substances is summarised in Table 1.3. The assessment of the risk to humans is based on a comparison between the estimated exposure and the established or suggested Acceptable Daily Intake (ADI). The asssessment of the risk to the environment is based on a comparison between the predicted environmental concentrations (PEC) in the aquatic environment and predicted no-effect concentrations (PNEC).

Physical-chemical properties and exposure

Several of the substances are considered to have lipophilic properties based on measured or estimated $LogP_{ow}$ values. Consequently they are expected to have a high tendency for accumulation in animals and plants.

Health assessment

Di(2-ethylhexyl) phosphate, tri(2-ethylhexyl) phosphate, tri-2-ethylhexyltrimellitate and dioctyl sebacate fulfil the criteria for classification with regard to acute toxicity or local effects. Based on the available literature di(2-ethylhexyl) phosphate should be classified as Corrosive (C) and Harmful (Xn) with the risk phrases R34 (Causes burns) and R21 (Harmful in contact with skin). This classification was suggested by Bayer AG (Bayer, 1993) and is supported by the toxicological findings in the literature. Tri(2-ethylhexyl) phosphate fulfils the criteria for classification as Irritant (Xi) with the risk phrase R36/38 (Irritating to eyes and skin) also according to Bayer AG (1993). Tri-2-ethylhexyltrimellitate fulfils the classification criteria with respect to acute toxicity as Harmful (Xn) with the risk phrase R20 (Harmful by inhalation) and dioctyl sebacate as Harmful (Xn) with the risk phrase R22 (Harmful if swallowed) based on LC_{50} and LD_{50} values. On the basis of the limited amount of data it has not been possible to evaluate all effects with respect to classification. For some of the substances data on effects from repeated dosing are available, but none of the investigated substances have been shown to cause serious systemic effects e.g. on organs, heredity, foetuses, or the like.

Environmental assessment

The compounds for which ecotoxicity data are available (only data for the aquatic environment available) show relativly high acute ecotoxicity, that in all cases would lead to an environmental hazard classification. The adipate would be ‘Very toxic’ (R50/53), epoxidised soybean oil is classifiable as ‘Toxic’ (R51/53), and o-acetyl tributyl citrate, di(2-ethylhexyl) phosphate and tri(2-ethylhexyl) phosphate would be classified as ‘Harmful’ (R52/53). For the trimellitate and the sebacate, the low aqueous solubility in combination with persistence and bioaccumulation potential would lead to a classification as ‘May cause long term effects in the aquatic environment’ (R53).

Several substances show limited degradabililty in the environment (the trimellitate and possibly both phosphates). Some have an estimated high bioaccumulation potential (citrate, trimellitate, dibenzoate and sebacate). The trimellitate and the dibenzoate possibly combine both these environmentally undesired properties. It must be emphasised that this is based on estimated values for bioaccumulation, which again are based on estimated octanol-water partition coefficients. It is possible that these compounds to some extent hydrolyses in the environment and bioaccumulation will then be considerably less. Measured bioaccumulation for the adipate and the two phosphates are below the criteria for when substances are considered to bioaccumulate.

Risk for humans

The risk to humans has been investigated in exposure scenarios illustrating direct exposure to products, e.g. tubes for haemodyalisis, milk tubes, and teething rings, and in relation to the workplace scenarios. The selected workplace scenario considers aerosol generation in connection with production of floor and wall coverings using a process temperature of 200°C and eight exposure events per day. The estimated concentrations in workplace air for the adipate in this scenario were 10^4 times the concentration, which has been shown to result in more pronounced reactions in workers with an allergy or asthma case history. For the two phosphates the estimated concentrations in workplace air were lower than reported concentrations from inhalation studies in the reveiwed literature. As no no-effect levels have been established for this type of exposure, the risk cannot be evaluated.

In relation to indirect exposure from the environment, the estimated concentration is compared to the Acceptabel Daily Intake (ADI) with food. Where no established ADI is available, it is chosen to compare the concentration to the group ADI established/suggested for for plasticisers (based on DEHP). For the sebacate the worst case exposure is expected to exceed the suggested ADI. For the trimellitate the exposure is expected to get close to or exceed the suggested group ADI.

When calculating the possible concentrations in food, it is especially root crops, which may contain considerable concentrations.

In a scenario where the exposure of children to teething rings is calculated, the citrate does reach 37% of a preliminary ADI of 1 mg/kg bw/day. This preliminary ADI is calculated by Nikiforov (1999) in relation to a preliminary risk assessment prepared on behalf of the manufacturer and it is not officially recognised. A closer investigation of the exposure conditions and better data on effects may change this evaluation.

Risk for the environment

None of the five assessed substances (diethylhexyl adipate, o-acetyl tributyl citrate, di(2-ethylhexyl) phosphate, tri(2-ethylhexyl) phosphate, and tri-2-ethylhexyl trimellitate) give rise to concentrations in the aquatic environment, which exceed the predicted no-effect level for the aquatic nvironment in general. For the adipate there may be a risk for the sediment compartment due to the sorptive properties of the substance combined with low degradability. The risk to the aquatic environment from o-toluene sulfonamide, epoxidised soybean oil, diisobutyrate and dioctyl sebacate could not be calculated.

Terrestrial and microbial toxicity

It must be stressed that a number of the assessed substances are lipophilic and may have a high affinity for sludge particles similar to that of DEHP. Data on terrestrial toxicity are not identified. Very limited information on effects on microorganisms in the sewage treatment was found for five substances plant (effects were typically not in the tested range of concentrations).

Data availability

The data availability varies among the suggested alternatives for phthalate plasticisers and materials. For di(2-ethylhexyl) adipate, o-acetyl tributyl citrate, tri(2-ethylhexyl) phosphate and tri-2-ethylhexyl trimellitate information is available covering a range of results from tests on toxicological properties. However, only di(2-ethylhexyl) adipate can be considered adequately covered, although some areas need further investigation. Di(2-ethylhexyl) phosphate, o-toluene sulfonamide, 2,2,4-trimethyl 1,3-pentandiol diisobutyrate, epoxidised soybean oil, dipropylene glycol dibenzoate and dioctyl se-

bacate are covered in less detail, either because of lack of information or because of inferiour quality of the tests.

For di(2-ethylhexyl)adipate a large number of studies are available covering acute toxicity, local effects, sensitisation, repeated dose toxicity, chronic toxicity, genetic toxicity, reproductive toxicity and carcinogenicity. Reviews discussing the toxicological profile of the substance are also available. In a substitution context it is however important to consider all areas which may give rise to concern, to make sure that only less hazardous substituents are introduced. Based on comparisons with the structural analogue, di(2-ethylhexyl) phthalate, for which the most critical effect is considered to be testicular toxicity, a need to address this issue for the adipate as well has been identified.

For o-acetyl tributyl citrate the available data are not sufficient for a profound assessment. Data on acute toxicity are sparse and other effects like carcinogenicity are not sufficiently covered for a qualified assessment.

For the two phosphates, di(2-ethylhexyl)phosphate and tri(2-ethylhexyl)phosphat, a number of studies are available, sufficient to suggest a classification of the substances for acute and local effects. Studies on lrepeated dose and chronic toxicity like reproductive toxicity and carcinogenicity are either not available or not sufficient for an assessment.

For tri-2-ethylhexyl trimellitate a number of studies are available covering acute and local effects. More details are however needed in order to classify the substance with regard to irritant effects. More data are also needed on repeated dose and chronic toxicity studies. Studies on reproductive toxicity are not covered at all in the reviewed literature.

O-toluene sulfonamide is sparsely covered in the literature and no data are found available on acute toxicity. Few studies are available on other effects, but not sufficient for a qualified assessment or classification. Human data are only available for related substances or combined products.

Few data are available for 2,2,4-trimethyl 1,3-pentandiol diisobutyrate. In order to make a proper evaluation of acute toxicity more detailed information is necessary. Repeated dose and chronic toxicity are not covered in the reviewed information.

A limited number of studies are available for epoxidised soybean oil. Studies on acute toxicity suggest low toxicity, but more detailed information is needed for a proper evaluation. Data on repeated dose toxicity and chronic effects as carcinogenicity are also insufficient for a qualified assessment.

No toxicological data have been found for dipropylene glycol benzoate.

Also dioctyl sebacate is sparsely covered in the available literature. Few data are available describing acute toxicity and only oral toxicity has been evaulated. Data on other effects are not sufficient for an evaluation.

No toxicological data have been found for polyester (polyadipate).

Regarding environmental properties only di(2-ethylhexyl) adipate, o-acetyl tributyl citrate, and tri(2-ethylhexyl) phosphate have a data set comprising algae, crustaceans and fish, and data on biodegradation. The remaining substances have very few or no ecotoxicological data. There are very few data

on chronic endpoints, very limited data on effects on microorganisms and no data on terrestrial ecotoxicity.

Table 1.2

The inherent properties for the investigated subtances are summarised using key parameters: acute and local effects, carcinogenicity(C), genetic toxicity (M), reproductive toxicity (R), sensitisation, persistance, bioaccumulation and aquatic toxicity. If data are not available for all parameters or only from non standard test results a tentative assessment is given (shown in parentheses). For the materials an evaluation is given based on general polymer properties. The symbols: ● identified potential hazard, ○ no identified potential hazard, and – no data available.

		Humans			Environment		
Name of substance	CAS No.	Acute and local effect (A/L)	CMR[d]	Sensitisation	Persistence	Bioaccumulation	Aquatic Toxicity
Diethylhexyl adipate	103-23-1	○/○	(○)[a]	○	○	○	● very toxic
O-acetyl tributyl citrate	77-90-7	○/○	○ M, R	○	● (inherent)	(●)	● (harmful)
Di(2-ethylhexyl) phosphate	298-07-7	●/●	○	○	● (conflicting)	○	● harmful
Tri(2-ethylhexyl) phosphate	78-42-2	(○)/●	○ M, C	-	●	○	● harmful
Tri-2-ethylhexyl trimellitate	3319-31-1	●/○	○	○	●	(●)	-
O-toluene sulfonamide	88-19-7	-/-	(○)[c]	-	(●)	○	-
2,2,4-trimethyl 1,3-pentandiol diisobutyrate	6846-50-0	-/-	-	-	-	-	-
Epoxidised soybean oil	8013-07-8	-/○	○	○	○	-	● toxic
Dipropylene glycol dibenzoate	27138-31-4	-/-	-	-	-[b]	(●)[b]	-[b]
Dioctyl sebacate	122-62-3	●/(○)	○	○	-	(●)	-
Polyadipates	-	-/-	-	-	- (persistent)	- (unlikely)	- (unlikely)
PU (MDI)	101-68-8	●/●	(○)	●	- (persistent)	- (unlikely)	- (unlikely)
LDPE	9002-88-4	-/-	-	-	- (persistent)	- (unlikely)	- (unlikely)

[a] Foetotoxicity (reduced ossification) has been identified as the most sensitive effect in a developmental toxicity study.

[b] QSAR estimates by Danish EPA leads to the classification N; R50/53 (May cause long term effects in the aquatic environment).

[c] A test on reproductive effects performed on a product containing OTSA as impurity attributes effect to OTSA. No substance specific data available.

[d] C,M,R indicated that the effect is investigated but no effects are seen.

Table 1.3
The evaluated risks to humans or the environment are summarised for the investigated substances (polymer materials not included). The estimated exposure of humans is compared to the Acceptable Daily Intake (ADI). Predicted environmental concentrations in the aquatic environment (PEC) are compared to predicted no-effect concentrations (PNEC). "Worst case" scenarios are used. The reader is referred to the main text and the data sheets for further explanations to the table. Parentheses show an assigned ADI. The symbols: ● ratio >1 (identified potential risk), ○ ratio <1 (no identified potential risk), and –no data available.

Substance	CAS no.	Ratio of dose to ADI		Ratio of PEC to PNEC		Remarks (ADI in mg/kgbw/d)
		Consumer from products	Humans via environment	Water	Sediment	
Diethylhexyl adipate	103-23-1	○	○	○	●	ADI 0.3
O-acetyl tributyl citrate	77-90-7	(○)[a]	(○)	○[b]	○[b]	Preliminary ADI 1.0[c]
Di(2-ethylhexyl) phosphate	298-07-7	○	○	○	○	Group ADI 0.05
Tri(2-ethylhexyl) phosphate	78-42-2	○	○	○	○	Group ADI 0.05
Tri-2-ethylhexyl trimellitate	3319-31-1	(○)	○	○[d]	○[d]	Assigned ADI 0.05
O-toluene sulfonic acid amide	88-19-7	(○)	(○)	-	-	Assigned ADI 0.05
2,2,4-trimethyl 1,3-pentandiol diisobutyrate	6846-50-0	-	-	-	-	No effect and exposure data
Epoxidised soybean oil	8013-07-8	-	-	-	-	No exposure data
Dipropylene glycol dibenzoate	27138-31-4	(○)	(○)	-	-	Assigned ADI 0.05
Dioctyl sebacate	122-62-3	○	●	-	-	Group ADI 0.05

[a] Dose reaches 37% of preliminary ADI in teething ring scenario.
[b] Tentative estimate based on only one ecotoxicity study.
[c] Preliminary ADI from Nikiforov (1999)
[d] Data set comprise only two acute values and one chronic NOEC value.

2 Sammenfatning på dansk

Phthalater og PVC

Phthalater er en gruppe blødgørere, der blandt andet anvendes til fremstilling af blød PVC. I de senere år har laboratorieforsøg vist, at nogle phthalater kan have toksikologiske og økotoksikologiske effekter, bl.a. skader på forsøgsdyrs forplantningsevne. Effekterne ses ved koncentrationer, der giver bekymring for udsættelsen af mennesker og miljø. Fem phthalater er under risikovurdering i EU. I Danmark blev der i 1999 igangsat en handlingsplan med det mål at opnå en 50% reduktion i anvendelse af phthalater over de næste 10 år. Andre lande, f.eks. Sverige og Tyskland, har en lignende målsætning. Det forventes derfor, at behovet for alternativer til de nuværende blødgørere vil stige i den nærmeste fremtid. I denne rapport er en række af alternativerne til phthalater og til blød PVC vurderet med hensyn til deres iboende egenskaber og potentielle risiko for mennesker og for miljø.

Vurdering af stoffer og materialer

Miljøstyrelsen havde i forvejen udvalgt fem stoffer, og der blev i samråd med industrien fastlagt yderligere seks stoffer som eksempler for de resterende grupper af alternative blødgørere. To polymer materialer blev valgt som alternativer til blød PVC. Datasøgning for stofferne er i første omgang foretaget i let tilgængelige databaser. På den baggrund er der udarbejdet foreløbige datablade for stoffernes fysisk-kemiske, sundheds- og miljømæssige egenskaber. Ved hjælp af information fra Produktregisteret, leverandører og industrien blev et muligt mønster for en forventet substitution af phthalater i Danmark udviklet.

Stoffer

- Diethylhexyl adipat
- O-acetyltributyl citrat
- Di(2-ethylhexyl) phosphat
- Tri(2-ethylhexyl) phosphat
- Tri-2-ethylhexyl trimellitat

Stofgrupper

- Alkylsulphonsyreestre
- Butanestre
- Polyester
- Epoxyester og epoxiderede olier
- Benzoater
- Sebacater

Polymer materialer

- Polyurethan
- Polyethylen

Exponering, sundheds- og miljøegenskaber

Nøgledata for vurderingen af toksikologiske effekter i mennesker og i miljøet blev identificeret. For disse data blev der hentet yderligere information i originallitteraturen, som er beskrevet mere detaljeret i selve rapporten.

Screening af miljø- og sundhedseffekter sker på iboende fareegenskaber. Risikoen for mennesker og miljø er belyst gennem to mulige eksponeringsscenarier: et scenarie er baseret på et forventet substitutionsmønster og det andet scenarie er baseret på, at hele anvendelsen af phthalater substitueres med den pågældende blødgører. Vurdering og sammenligning er udført i overensstemmelse med principperne i EU Technical Guidance Document. Eksponeringerne er fundet ved anvendelse af EASE og EUSES modellerne, som blev forsynet med stoffets relevante data og med mængder for det val-

gte eksponeringsscenarie. De fysiske dimensioner i det regionale scenarie repræsenterer danske forhold.

Tabel 2.1
Stoffernes anvendelse til blødgøring er allerede registreret i udvalgte produktgrupper. Data er fra Produktregisteret. Polyester blødgøreren (polyadipat) er ikke inkluderet pga. manglende CAS nr.

CAS Nr.	Navn (synonym anvendes eventuelt i Produktregisteret)	Filler	Maling og lak	Klæbemidler	Trykfarver	Plast i beton	Gummiprodukter	PVC pakninger
103-23-1	Di(ethylhexyl) adipat	•	•	•		•	•	
77-90-7	O-acetyl tributyl citrat				•	•		
298-07-7	Di(2-ethylhexyl) phosphat							
78-42-2	Tri(2-ethylhexyl) phosphat	•	•	•		•		
3319-31-1	Tri-2-ethylhexyltrimellitat *							
88-19-7	Alkylsulfonsyreester *							
6846-50-0	Butanester (2,2,4-trimetyl 1,3-pentanedioldiisobutyrat	•	•		•	•		•
8013-07-8	Epoxideret sojabønne olie	•	•	•	•			•
27138-31-4	Dipropylen glycol dibenzoat				•			
122-62-3	Dioctyl sebacat			•				

* Ikke registreret til dette formål i Produktregisteret.

Migration og fordampelighed

Nøgleparametre med hensyn til frigivelse af blødgører under polymerproduktion og forbrugerens anvendelse af produkter er fordampelighed og migration fra PVC materialet. Der er fundet data for fordampelighed for mange stoffer, men kun få sammenlignelige data er identificeret for migrationspotentiale.

Vurdering af polymermaterialer

Vurderingsprincipperne i EU Technical Guidance Document finder kun anvendelse på enkeltstoffer. Polyesterblødgøreren og de to materialer er vurderet på grundlag af deres monomeres, oligomeres og polymeres generelle egenskaber. På baggrund af de indhentede data er det vurderet at polyadipaten og de to materialer (low density polyethylen og polyurethan) ingen umiddelbare effekter vil have i forbrugersituationen eller i miljøet.

Vurdering af stoffer

En sammenlignende vurdering af stofferne er vanskelig, da der for nogle af stofferne kun er få og ofte forskellige parametre til rådighed. Kvantitativ ranking er ikke mulig med det tilgængelige datasæt for stofferne. I de efterfølgende to tabeller (tabel 2.2 og tabel 2.3) præsenteres en opsummering af de farlige iboende egenskaber og den potentielle risiko ved anvendelse af de foreslåede alternativer.

De valgte nøgleegenskaber (iboende egenskaber) med hensyn til mennesker er de effekter, som ses umiddelbart efter eksponering samt kroniske effekter, der kan opstå efter en enkelt eller gentagen eksponering. For disse egenskaber er det vurderet hvorvidt de opfylder kriterierne for klassifikation i overensstemmelse med EU's klassifikationskriterier. Nøgleegenskaber med hensyn til miljøet er persistens, bioakkumulation og akvatisk toksicitet. For

disse parametre er det ligeledes vurderet om de opfylder EUs klassifikationkriterier for det akvatiske miljø.

Vurderingen af risikoen for mennesker og miljø i forbindelse med de undersøgte stoffer er opsummeret i tabel 2.3. Vurderingen af risikoen for mennesker er baseret på en sammenligning af den beregnede udsættelse og den fastlagte eller foreslåede accepterede daglige indtagelse (ADI). Vurderingen af risikoen for miljøet er baseret på en sammenligning af beregnede koncentrationer i vandmiljøet og fastlagte nul-effektniveauer.

Fysisk-kemiske egenskaber og eksponering

Flere af stofferne er vurderet til at have lipofile egenskaber baseret på målte eller beregnede oktanol-vand fordelingskoefficienter. Det må derfor forventes, at de kan have en stor tilbøjelighed til ophobning i dyr og planter.

Sundhedsvurdering

Di(2-ethylhexyl) phosphat, tri(2-ethylhexyl) phosphat, tri(2-ethylhexyl)trimellitat og dioctyl sebacat opfylder klassifikationskriterierne for akut toksicitet eller lokal effekt. Baseret på den tilgængelige litteratur kan di(2-ethylhexyl)phosphat klassificeres som "Ætsende" (C) og "Sundhedsskadelig" (Xn) med risikosætningerne "Ætsningsfare" (R34) og "Farlig ved hudkontakt" (R21). Denne klassificering er foreslået af Bayer AG (Bayer, 1993) og støttes af den toksikologiske litteratur. Tri(2-ethylhexyl) phosphat opfylder kriteriet for "Lokalirriterende" (Xi) med risikosætningen "Irriterer øjnene og huden" (R36/38) også i følge Bayer AG (1993). Tri(2-ethylhexyl)trimellitat opfylder kriterierne med hensyn til akut toksicitet for "Sundhedsskadelig" (Xn) med risikosætningen "Farlig ved indånding" (R20), og dioctylsebacaten opfylder kriteriet for "Sundhedsskadelig" (Xn) med risikosætningen "Farlig ved indtagelse" (R22) baseret på LC_{50} og LD_{50} værdier. På grundlag af det begrænsede datasæt har det ikke været muligt at vurdere alle effekter med hensyn til klassificering. For nogle stoffer findes data om effekter ved gentagen og langvarig eksponering, men ingen af de undersøgte stoffer er påvist at give alvorlige systemiske skader på organer, arveanlæg, fosterskader eller lign.

Miljøvurdering

For de stoffer, der findes data for (kun data for vandmiljøet tilgængelige), er toksicitet i miljøet relativt høj, idet de alle ville kunne klassificeres. Adipaten falder i kategorien "meget giftig"(R50/53) og epoxideret sojabønne olie har akut toksicitet i kategorien "giftig" (R51/53). O-acetyl tributyl citrat,di(2-ethylhexyl) phosphat og tri(2-ethylhexyl) phosphat falder i kategorien "skadelig" (R52/53). For trimellitaten og sebacaten kan den ringe vandopløselighed i kombination med persistens og bioakkumulationspotentiale lede til klassifikation som "Kan forårsage uønskede langtidseffekter i vandmiljøet" (R53).

Flere stoffer viser tegn på ringe nedbrydelighed i miljøet (mellitaten og muligvis begge phosphater). Nogle har et højt estimeret bioakkumulationspotentiale (citraten, trimellitaten, dibenzoaten og sebacaten). Trimellitaten og dibenzoaten kombinerer muligvis begge disse miljømæssigt uønskede egenskaber. Det skal dog understreges, at der er tale om estimerede værdier for bioakkumulering baseret på estimerede oktanol-vand fordelingskoefficienter. Det er muligt, at disse stoffer i et ukendt omfang hydrolyseres i miljøet og bioakkumuleringen vil da være betydelig mindre. Målt bioakkumulation for adipaten og de to phosphater overskrider ikke kriteriet for, hvornår stoffer anses for bioakkumulerbare.

Risiko for mennesker

Risikoen for mennesker er undersøgt i eksponeringsscenarier ved direkte udsættelse fra produkter, eks. fra slanger til dialyse, malkeslanger og bider-

inge og ved udsættelse i arbejdsmiljøet. Det valgte arbejdsmilljøscenarie omhandler aerosoldannelse i forbindelse med produktion af gulv- og vægbeklædning ved en procestemperatur på 200°C og otte eksponeringshændelser pr. dag. De beregnede luftkoncentrationer for adipaten ved dette scenarie var 10^4 gange højere end den koncentration, som i en undersøgelse gav kraftigere reaktioner hos arbejdere med en eksisterende astma eller allergi. For de to phosphater var de estimerede luftkoncentrationer i arbejdsmiljøet lavere end de rapporterede koncentrationer fra inhalationsstudier. Der er dog ikke fundet nul-effekt niveauer ved denne type eksponering og risikoen er derfor vanskeligt at vurdere.

Ved indirekte udsættelse for stoffet via miljøet er den forventede koncentration sammenlignet med den accepterede daglige indtagelse (ADI) med fødevarer. Hvis ingen ADI var tilgængelig er en default-værdi på 0.05 mg/kg bw/dag tildelt blødgørere på baggrund af DEHPs værdi og symbolet vises i parentes i Tabel 2.3. Dette er samme værdi som "Group value" der anvendes for blødgører i materialer i kontakt med fødevarer i EU. For sebacaten forventes udsættelsen i værste tilfælde at overskride den foreslåede ADI. For trimellitaten vil udsættelsen nærme sig eller overstige den foreslåede ADI gruppeværdi.

Ved beregning af mulige koncentrationer i fødevarer, er det især rodfrugter som kan indeholde store koncentrationer.

I et scenarie hvor udsættelsen af børn fra bideringe er beregnet, giver citraten en koncentration på 37% af den foreløbige fastsatte ADI på 1 mg/kg/dag. Den foreløbige ADI er beregnet af Nikiforov (1999) i forbindelse med en foreløbig risikovurdering udført for producenten og er ikke officielt anerkendt. En nærmere undersøgelse af eksponeringsforholdene og bedre data om effekter kan ændre denne vurdering.

Risiko for miljøet

Ingen af de fem vurderede stoffer (diethylhexyladipat, o-acetyltributyl citrat, di(2-ethylhexyl)phosphat, tri(2-ethylhexyl)phosphat og tri(2-ethylhexyl)trimellitat) giver koncentrationer i vandmiljøet, som overskrider det beregnede nul-effekt niveau i vandmiljøet generelt. For adipaten kan der være en risiko i sediment-delmiljøet på grund af stoffets tilbøjelighed til at binde sig til partikler kombineret med en ringe nedbrydelighed. Risikoen i vandmiljøet kunne ikke beregnes for o-toluensulfonamid, epoxideret sojabønneolie, diisobutyraten eller sebacaten.

Terrestrisk og mikrobiel toksicitet

Det skal understreges, at flere af de vurderede stoffer er lipofile og kan have en høj affinitet for slampartikler i lighed med DEHP. Der er ikke fundet data for terrestrisk toksicitet, og meget begrænset information om effekter på mikroorganismer i renseanlæg er identificeret for fem stoffer (effekt er typisk ikke fundet i det undersøgte koncentrationsinterval).

Tilgængelige data

Der er en ret varierende mængde data til rådighed for de vurderede alternativer til phthalat blødgører pg blød PVC. For di(2-ethylhexyl)adipat, o-acetyltributylcitrat, tri(2-ethylhexyl)phosphat og tri(2-ethylhexyl)trimellitat er der information fra test som dækker en bred vifte af toksikologiske egenskaber. Det er imidlertid kun di(2-ethylhexyl)adipat som er acceptabelt dækket i forhold til en generel vurdering, selvom der stadig er områder som kræver yderligere undersøgelser. Di(2-ethylhexyl)phosphat, o-toluensulfonamid, 2,2,4-trimethyl-1,3-pentandioldiisobutyrate, epoxidiseret sojabønne olie, dipropylenglycoldibenzoat og dioctylsebacat kan ikke vur-

deres i samme omfang, som de førnævnte, enten på grund af manglende data eller fordi studierne er for ringe beskrevet.

For diethylhexyl adipat er et stort antal studier tilgængelige til beskrivelse af akut toksicitet, lokale effekter, sensibilisering, toksicitet ved gentagen eksponering, genetisk toksicitet, reproduktionstoksicitet og carcinogenicitet. Oversigtsartikler, som beskriver stoffets toksikologiske profil er ligeledes tilgængelige. I forbindelse med substitution er det dog vigtigt at tage højde for alle områder, der kan give anledning til betænkelighed, for at sikre at kun substituenter, som må anses for mindre sundhedsfarlige bliver introduceret. Baseret på sammenligninger med det strukturelt analoge stof, diethylhexyl phthalat, som anses for at have testikulær toksicitet, som den kritiske effekt, er der derfor identificeret et behov for belysning af denne effekt i relation til adipaten.

For o-acetyl tributyl citrat er de tilgængelige data ikke tilstrækkelige til en grundig vurdering. Data for akut toksicitet er begrænsede og øvrige effekter som carcinogenicitet er ikke tilstrækkeligt belyst til at foretage en endelig vurdering.

For de to phosphater er der tilstrækkeligt datagrundlag til at foreslå klassificering af stofferne med hensyn til akutte og lokale effekter. Studier til belysning af effekter som reproduktionstoksicitet og kræftfremkaldende egenskaber er enten ikke tilgængelige eller utilstrækkelige til at foretage en endelig vurdering.

Der er fundet en række studier til belysning af akutte og lokale effekter af tri(2-ethylhexyl)trimellitat. Flere detaljer er dog nødvendige med henblik på klassificering af stoffet for irriterende effekter. Flere data er ligeledes nødvendige for at vurdere øvrige effekter og for reproduktionstoksiske effekter er der ikke fundet data overhovedet i den gennemgåede litteratur.

O-toluen sulfonamid er kun begrænset beskrevet i litteraturen og ingen data er fundet tilgængelige for akut toksicitet. Få studier til belysning af andre effekter er fundet, men ikke tilstrækkelige til en kvalificeret vurdering af effekterne. Humane data er kun tilgængelige for lignende stoffer eller stofkombinationer.

For 2,2,4-trimethyl 1,3 pentandiol diisobutyrat er der ligeledes få tilgængelige data. Til en vurdering af de toksikologiske egenskaber er mere detaljeret information nødvendig. Gentagen eksponering (andre effekter) er ikke omfattet af den litteratur, som er fundet for stoffet.

Et begrænset antal studier er fundet til belysning af epoxideret sojabønne olie. Tests af akutte effekter tyder på lav toksicitet, men mere detaljeret information er nødvendig med henblik på en grundig vurdering. Data for toksicitet ved gentagen eksponering og kroniske effekter er ligeledes utilstrækkelige til en kvalificeret vurdering.

Der er ikke fundet toksikologiske data for dipropylenglycol benzoat.

Dioctyl sebacat er også utilstrækkelig belyst i den gennemgåede litteratur. Få data beskriver akut toksicitet og kun akutte effekter ved indtagelse er vurderet. Data for øvrige effekter er ikke tilstrækkelige til en vurdering.

Der er ikke fundet toksikologiske data for polyesteren (polyadipat).

Med hensyn til data for økotoksicitet er di(2-ethylhexyl)adipat, o-acetyltributylcitrate og tri(2-ethylhexyl)phosphat de eneste som har et datasæt som både omfatter alger, krebsdyr og fisk, og information om bionedbrydelighed. De øvrige stoffer har få eller ingen data om miljømæssige egenskaber. Der er meget få data fra studier af kroniske effekter, meget begrænsede data om effekter på mikroorganismer og ingen data på terrestrisk økotoksicitet.

Tabel 2.2

De iboende egenskaber for de undersøgte stoffer er opsummeret ved anvendelse af nøgleparametre: akut og lokal effekt, kræftfremkaldende (C), skader på arveanlæg (M), skader på fostre eller forplantningsevnen (R), sensibilisering, nedbrydelighed, ophobning og giftighed i vand. Hvis der ikke er data tilgængelige for alle parametre eller data er fra ikke standardiserede test er der givet en anslået vurdering (vist i parenteser). For materialerne er der givet en evaluering baseret på generelle polymer egenskaber. Symbolerne betyder ● potentiel fare identificeret, ○ ingen potentiel fare identificeret, og – ingen data tilgængelige.

		Mennesker			Miljø		
Stofnavn	CAS Nr.	Akut og lokal effekt (A/L)	CMR[e]	Sensibi-lisering	Persistens	Bioakku-mulation	Toksicitet i vand
Diethylhexyl adipat	103-23-1	○/○	(○)[a]	○	○	○	● meget giftig
O-acetyl tributyl citrat	77-90-7	○/○	○ M, R	○	● (iboende)	(●)	● (skadelig)
Di(2-ethylhexyl) phosphat	298-07-7	●/●	○	○	(●)[d]	○	● skadelig
Tri(2-ethylhexyl) phosphat	78-42-2	(○)/●	○ M, C	-	●	○	● skadelig
Tri-2-ethylhexyl trimellitat	3319-31-1	●/○	○	○	●	(●)	-
O-toluene sulfonamid	88-19-7	-/-	(●)[c]	-	(●)	○	-
2,2,4-trimethyl 1,3-pentandiol diisobutyrat	6846-50-0	-/-	-	-	-	-	-
Epoxideret so-jabønne olie	8013-07-8	-/○	○	○	○	-	● giftig
Dipropylene gly-col dibenzoat	27138-31-4	-/-	-	-	-[b]	(●)[b]	-[b]
Dioctyl sebacat	122-62-3	●/(○)	○	○	-	(●)	-
Polyadipat	-	-/-	-	-	- (persistent)	- (usandsyn-lig)	- (usandsyn-lig)
PU (MDI)	101-68-8	●/●	(○)	●	- (persistent)	- (usandsyn-lig)	- (usandsyn-lig)
LDPE	9002-88-4	-/-	-	-	- (persistent)	- (usandsyn-lig)	- (usandsyn-lig)

[a] Foster toksicitet (reduceret ossificering) er identificeret som den mest følsomme effekt i udviklingsstudie i rotter.
[b] QSAR estimat af Miljøstyrelsen leder til klassificering N; 50/53 (kan forårsage uønskede langtidsvirkninger i vandmiljøet)
[c] Data fra test på produkter, ingen stofspecifik information
[d] Uoverensstemmelse i datasæt
[e] C,M,R angiver at det er undersøgt, men at der ikke er set effekter

Tabel 2.3

Vurderet risiko for mennesker eller miljø er opsummeret for undersøgte stoffer (polymere materialer er ikke medtaget). Den en beregnede udsættelse af mennesker er sammenlignet med den accepterede daglige indtagelse(ADI). Beregnede koncentrationer i vandmiljøet (PEC) er sammenlignet med nul-effektniveauer (PNEC). "Worst case scenarier" er anvendt. Der henvises til hovedteksten og til datablade for yderlige forklaring og forudsætninger. Parenteser angiver en tildelt ADI. Symbolerne betyder: ● >1(potentiel risiko identificeret), ○ <1 (ingen potentiel risiko identificeret), og – (ingen data tilgængelige).

		Ratio af dosis til ADI		Ratio af PEC til PNEC		
Stof	CAS nr.	Forbruger fra pro-dukter	Mennesker via miljøet	Vand	Sediment	Bemærkning
Diethylhexyl adipat	103-23-1	○	○	○	●	ADI 0,3
O-acetyl tributyl citrat	77-90-7	(○)[a]	(○)	○[b]	○[b]	Foreløbig ADI 1,0[c]
Di(2-ethylhexyl) phosphat	298-07-7	○	○	○	○	Group ADI 0,05
Tri(2-ethylhexyl) phosphat	78-42-2	○	○	○	○	Group ADI 0,05
Tri-2-ethylhexyl trimellitat	3319-31-1	(○)	(●)	○[d]	○[d]	Tildelt ADI 0,05
O-toluensulfonamid	88-19-7	(○)	(○)	-	-	Tildelt ADI 0,05
2,2,4-trimetyl 1,3-pentandiol diisobutyrat	6846-50-0	-	-	-	-	Ingen effekt og eksponer-ingsdata
Epoxideret sojabønner olie	8013-07-8	-	-	-	-	Ingen eksponer-ingsdata
Dipropylen glycol dibenzoat	27138-31-4	(○)	(○)	-	-	Tildelt ADI 0,05
Dioctyl sebacat	122-62-3	○	●	-	-	Group ADI 0,05

[a] Dosis når 37% af preliminær ADI i bidering scenario.
[b] Tentativt estimat baseret på en enkelt økotoksicitetsstudie.
[c] Preliminær ADI fra Nikiforov (1999)
[d] Datasæt omfatter to akutte studier og et kronisk NOEC studie.

3 Introduction and approach

3.1 Background

A total of 20 million tonnes of PVC is produced globally every year. Recent statistics from the Association of European Plastic Converters states that production in Western Europe is 4.2 million tonnes of rigid and 3.7 million tonnes of flexible PVC (EU Commission 2000).

Plasticisers are necessary to manufacture flexible PVC products and may in the product constitute from 15 to 60% (Gächter, Müller 1993) depending on the final application with a typical range between 35 - 45%. At present a range of phthalates constitute the vast majority of plasticisers for PVC (in 1997: 93%) and approximately 900,000 tonnes are used annually in Western Europe. Other plasticisers, in particular adipates, trimellitates, organophosphates and epoxidised soy bean oil can also be used in PVC, but constitutes only a fraction of the present total consumption (EU Commission 2000).

Five of the phthalates have been put on priority lists for risk assessment due to the potential for human health and environment effects, and some are already under assessment by the EU. In Denmark an action plan has been adopted to reduce the use of phthalates with 50% over the next 10 years. In Sweden the usage of the main phthalate DEHP (diethylhexylphthalate) is to be reduced, and in Germany the Umweltbundesamt recommends a phase-out of flexible PVC where safer alternative exist. It is therefore expected that the need for alternatives to the existing plasticisers will grow.

The present project is a general assessment of the use, exposure, and possible health and environmental effects of several alternative plasticisers and of two materials suggested for substitution of flexible PVC.

3.2 Approach

The DEPA has presented a list of substances and groups of substances for the study, which were suggested as possible alternatives to phthalate plasiticisers, and two materials suggested as alternatives to flexible PVC. A health and environmental assessment, including exposure, was requested. The list comprised:

Substances

- Diethylhexyl adipate
- O-acetyltributyl citrate
- Di(2-ethylhexyl) phosphate
- Tri(2-ethylhexyl) phosphate
- Tri-2-ethylhexyl trimellitate

Groups of substances

- Alkylsulphonic acid esters
- Butane esters
- Polyester
- Epoxyester and epoxydized oils
- Benzoates
- Sebacates

Materials

- Polyurethane
- Polyethylene

In the following an overview of procedures and activities of the assessment is presented. A more detailed description is given in the introduction to the presentation of the result of each activity.

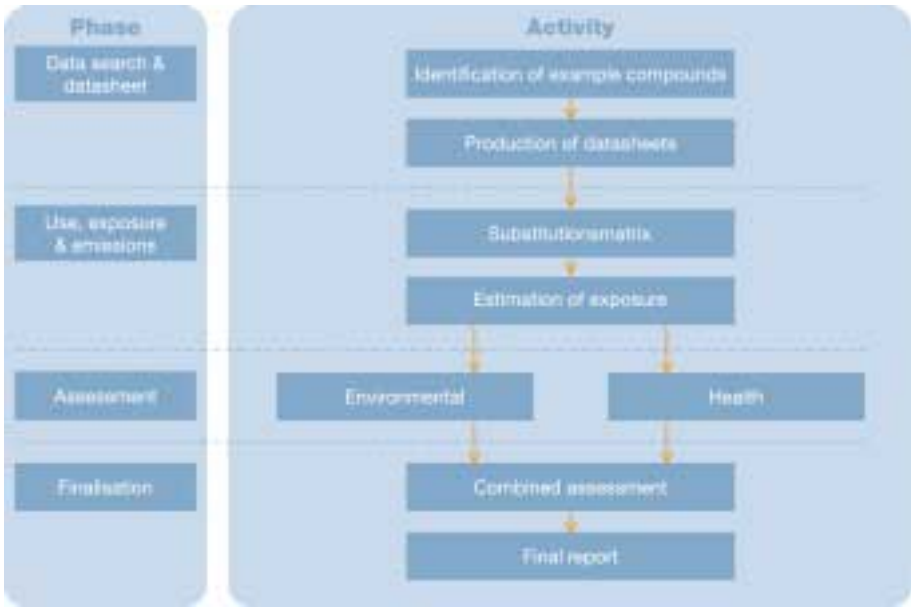

Figure 3.1
Overview of procedures and activities of the assessment.

3.2.1 Data search and substance selection

Identification of phthalate usage

The selection of example substances and materials were based on information on the present uses of phthalates, i.e. information from the industry and from The Danish Product Register (PR). Especially, the usage as plasticiser was emphasised.

Use estimation

The use of PVC and phthalates herein was taken from the report on mass balance of phthalates for Denmark from 1996 (Hoffmann 1996) and from the Inventory of the Industry (2000).

Preliminary data on substance properties

From a number of databases and other readily available information sources preliminary data collection on properties was performed on the five substances and on a number of suggestions for additional substances as examples for groups of substances. This information was compiled into data sheets and given a preliminary review.

Selection of substances for assessment

Based on the information on use pattern, volume, and the screening data, six substances were chosen as examples of their group and for this total of 11 substances a more comprehensive data collection took place.

3.3 Properties information

3.3.1 Data collection

Databases used

The data collecting includes searches for original literature in bibliographical databases and searches in the following databases directed towards relevant toxicological and ecotoxicological properties.

- Chemfinder, CHEMFATE, ENVICHEM, TOXALL
- ECOTOX: Aquire, Terretox, Phytotox
- Hazardous Substances Data Bank (HSDB)
- Oil and Hazardous Material Technical Assistance Data System

- International Uniform Chemical Information database (IUCLID)
- Handbook of environmental data of organic chemicals ("Verschueren")
- SAX's Dangerous properties of industrial materials

The most relevant reference sources from the listed database outputs have in addition been procured. In most cases these references are reviewed literature and not the original sources. This means that the evaluated effects are not always described in detail but often in more general terms like 'slightly irritating' or 'moderately toxic'. A more precise evaluation is therefore not possible and also not a precise evaluation against the classification criteria in the Substance Directive (EU, 1967).

Quality assessment of data for the environmental hazards of chemicals is based on the procedures in Pedersen et al. (1995).

3.3.2 Estimation of exposure

Worst case

As a first step, a hypothetical worst case scenario was included for each substance assuming a total change of all phthalate consumption to one single substitute. This number was also used in exposure calculation.

Substitution matrix

Estimation of exposure in a future substitution scenario was attempted by establishing a 'realistic' use pattern scenario for all the substitutes in PVC applications. This was performed with a substitution matrix showing the use pattern in use groups. From this matrix the maximum usage in tonnes for an application was used for the exposure calculation.

Exposure

The exposure was calculated for workers, consumers, humans exposed via the environment and the aquatic and terrestrial environment by using the EUSES programme (European Chemicals Bureau 1996) based on the EU Technical Guidance Document on risk assessment of chemicals (EU 1996).

3.3.3 Assessment

Where incomplete information on physical-chemical, toxicological or ecotoxicological properties was identified in data sheets a renewed information search was performed.

Health

The health assessment is based on available data from animal studies reflecting all relevant exposure routes and toxicological effects. Observations in humans are included where available. These data are presented in the data sheets included in Appendix 1. In the data sheets the most significant test results are highlighted (marked with ♦) and these results are presented in chapter 5 along with an evaluation of each substance. Calculations using the EASE model are used to estimate the possible exposure from selected use scenarios in the work environment and to the consumer. The estimated exposure is compared to the doses and effects seen in the described animal studies and to the exposure levels and related effects observed in humans.

Environment

The environmental assessment is built around the exposure data provided by the EUSES for a number of compartments for which relevant ecotoxicological test data have been searched. These include test with algae, crustaceans and other invertebrates, fish, micro-organisms, and terrestrial organisms. Other test data have also been included where relevant. For each of these groups of organisms the data are presented in the datasheets provided in the appendix and the key data for the assessment are marked. A more detailed description of the key data is presented in chapter 5 along with a summary

description of the substance data. The (eco)toxicolgical data are not entered into EUSES, because of a typical lack of the type of test data needed to comply exactly with EUSES. The risk is estimated by comparing predicted environmental concentrations (PEC) and predicted no-effect concentrations (PNEC).

The parameters on partitioning and degradation are also discussed under 'Environment'. These values also enter EUSES and influence the exposure calculations. These are octanol-water partition coefficient, bioconcentration factor (BCF), soil or sediment-water partition coefficient, and aerobic and anaerobic biodegradation.

3.3.4 Combined assessment

The sources of the data are given primarily in the data sheets in the report appendix and for core information also in the main report. The information includes peer reviewed original papers, databases, previous reviews and reports, books, and proprietary information from suppliers. The combined assessment is found in chapter 7.

It has been attempted to prioritise studies performed after standard test methods and guidelines for inclusion. In a number of cases the database IUCLID, which contains information submitted by the industry, is almost the sole data source. Again, standardised tests have been selected whenever possible.

The core physical-chemical properties considered are the hazardous properties, such as corrosiveness, flammability etc.

The choice of properties for human toxicity has been based on the hazard indicators for humans as mentioned in CSTEE (2000), i.e. carcinogenicity, reproductive and developmental effects, mutagenicity, sensitisation and severe organ toxicity supplemented with assessment of acute and/or local effects. For the environment the properties evaluated are the three core properties of the hazard classification scheme of EU (Commission of the European Communities 1993), i.e. persistence (biodegradation), bioaccumulation and acute toxicity to algae, crustaceans and fish of the chemical substance.

In addition to evaluating hazards, the risk is also assessed. For humans this is achieved by comparing the estimated dose of the substance in consumer and environmental exposure with existing or estimated acceptable daily dose (ADI). For the environment the environmental risk quotient is calculated from PNEC and estimated environmental concentrations.

Other important properties with respect to the potential use areas of the substances and materials are the volatility and migratory properties. Comparison of these properties will also be carried out, although no recommendation regarding technical uses will be made.

4 Use patterns and substitutes

4.1 Use patterns of phthalates

4.1.1 Assessment of use of phthalate plasticisers

Many polymer products need to be flexible and soft so they can take on a different shape and form depending on their application. This plastification is often conducted using plasticisers such as phthalates, adipates, trimellitates and citrates.

The major uses of flexible PVC in Western Europe is in the product groups of film and sheet, wire and cable, floor covering, extrusions, coated fabrics and plastisols (European Council for Plasticisers and Intermediates, 2000).

PVC plasticisers

According to the European Council for Plasticisers and Intermediates there are more than 300 different types of plasticisers of which about 50-100 are in commercial use (European Council for Plasticisers and Intermediates, 2000). The most commonly used plasticisers are phthalates.

In the Danish Product Register, close to 180 different plasticisers are registered in a wide range of products.

According to the European industry 95% of the plasticiser production is for PVC end-use. In Denmark phthalate in PVC contributes with 90% of the turnover of phthalates (Hoffmann, 1996).

Plasticisers are used in a wide range of products from toys, babycare items, medical devices, wall-coverings, electrical cables, automotive parts, packaging, coatings and in the manufacture of clothing and footwear.

Smaller quantities of plasticisers are also used in paints, rubber products, adhesives and some cosmetics. A small amount is used as denaturant in cosmetics such as "sun-tan oil".

In Denmark, phthalates are used as plasticisers in various PVC-products for medical utilities, packaging, cables, fittings, floor/wall covering, but there is still a an extensive, not specified, consumption of phthalates in plasticised PVC products (Hoffmann, 1996). This "Other application of PVC" covers e.g. the use of phthalates in plastisol (coating materials) and toys. Artificial leaders are e.g. produced by coating textile with plastisol. The plastisol consists of a PVC-resin, solvent and a plasticiser e.g. phthalates.

In Denmark, phthalates are used as plasticisers in non-PVC materials such as lacquer, paint, printing inks, adhesives, fillers and denaturants in cosmetics. The unspecified consumption of phthalates in non-PVC applications is small compared to the use in PVC (Hoffmann, 1996). Capacitors with dielectric fluid may contain phthalates (notably DEHP), but in Denmark most capacitors are dry and therefore without fluids. Another use of phthalates in non-PVC products is in ceramics for electronic products. It is assumed that the used amounts associated with these applications are relatively small in Denmark.

The use of phthalates as plasticisers a.o. in 1992 in Denmark was assessed in the Substance Flow Analysis (Hoffmann, 1996). This analysis indicates

that the Danish distribution of the applications of phthalates in 1992 can be illustrated as in Figure 4.1.

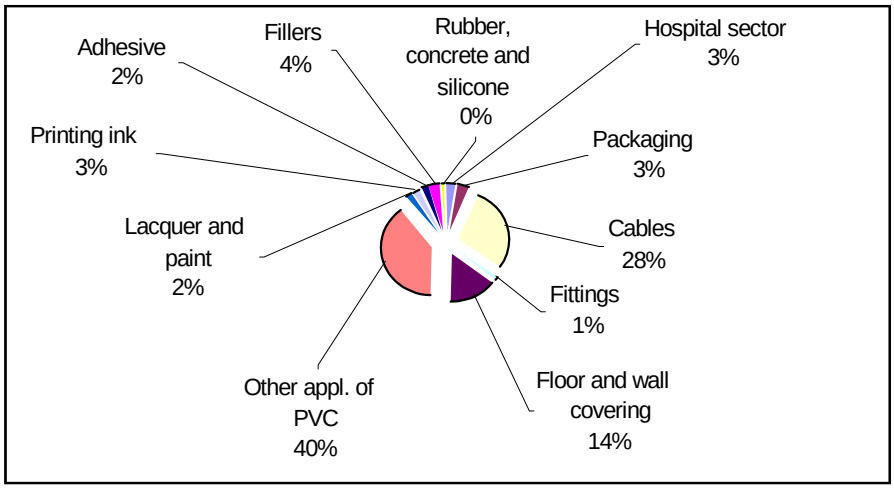

Figure 4.1
The distribution of phthalates for applications in Denmark in 1992 (Hoffmann, 1996).

As mentioned earlier, the use of phthalates in PVC-toys is included in "other applications of PVC". This amount is assumed equal to the use of DEHP for flexible PVC-toys. This includes phthalates used for toys for children both less and more that 3 years old ~ 380 ton/year. The use of phthalates are now banned for the former category.

It appears that the amount of phthalates within certain applications is decreasing. This trend is illustrated in Table 4.1, where the development in the use pattern is listed.

Table 4.1
Development in the use pattern of phthalates in different applications in Denmark.

Application	Subapplication	Amount phthalate in 1992 in tonnes[a]	Amount phthalate in 1994 in tonnes[b]	Est. amount of phthalate in 2000 in tonnes[c]	Trend
PVC	Medical utilities	240-350	240		increasing [a]
	Packaging	200-350	100		decreasing [a]
	Construction and installations:				
	- cables	3,000	3,500		constant [a]
	- fittings	80	700		constant [a]
	- floor and wall covering	1,500	2,000		increasing [a]
	other application	4190	3,100		[e]
	Subtotal	9,200-9,500	9,640		[d]
Non-PVC	Lacquer and paint	45-225	189[g]	70	decreasing [a and c]
	Printing ink	90-270		50	decreasing [a and c]
	Adhesives	160-220	350[g]	220	constant [c]
	Fillers	< 400		100	decreasing [c]
	Denaturants	< 5			? [a]
	Other non-PVC applications e.g. in rubber, concrete and silicone	< 50[f]			? [a]
Total		9,500-10,700	11,000		

[a] Hoffmann (1996)
[b] The Danish Plastics Federation (1996)
[c] Hansen and Havelund (2000)
[d] At the moment increasing globally and constant on the Nordic market, but decreasing a little on the Danish marked.
[e] According to SFA (Hoffmann, 1996) consumption is decreasing but according to the Danish Plastics Federation (1996) it might be increasing.
[f] The application "other applications" under non-PVC -products in Hoffmann (1996) is estimated to cover as a maximum 50 tons.
[g] Inventory for the Consumption in 1994 made by FDLF for The Danish EPA.

The trend shown in Table 4.1 for the non-PVC-products, is a decline in the consumption of phthalates. Concerning the PVC-products the general trend is difficult to deduce from Table 4.1. According to the suppliers the overall consumption is at the moment increasing but within the near future it is expected to decline.

The consumption of phthalates is slightly increasing in the EU as a whole, stagnant in northern Europe, and decreasing slowly in Denmark (Hansen and Havelund, 2000).

4.2 Selection of substitute substances

In the following the background for the selection of the 11 substitutes for phthalates is described. In Table 4.1 a total of 18 compounds are listed that, in variable degree, all are potential substitutes for phthalates.

- 5 chemical compounds (substitutes), and
- 6 groups of substances.

Within each of the 6 groups, one specific substance has been selected as marker for the group.

The primary source of information is the industry and the initial information from The Danish Product Register.

To get an impression of how the substitution will take place selected industrial organisations have been contacted. Suppliers and users of phthalates and/or have been contacted to give an estimate of how a complete substitution of phthalates 5 years from here can be predicted.

The same substance will not substitute phthalates in all applications. The substitution will within the different applications take place by a distribution of substitutes. Estimates of this distribution are given in the substitution matrix in Table 4.1 and Table 4.2.

In Table 4.1, a short description of the selection of substitutes for phthalates for various applications is given.

Table 4.1
The plasticiser substitutes and suggestions for example substances in the groups of plasticisers. Other possible substitutes are shown in italics.

Group of plasticiser	Name of substance	CAS No.
Adipate	Diethylhexyl adipate	103-23-1
	Diisodecyl adipate	*27178-16-1*
	Diisooctyl adipate	*1330-86-5*
Citrate	O-acetyltributyl citrate	77-90-7
Phosphate	Di(2-ethylhexyl) phosphate	298-07-7
	Tri(2-ethylhexyl) phosphate	78-42-2
Mellitate	Tri-2-ethylhexyl trimellitate	3319-31-1
Alkylsulphonic acid esters	o-Toluene sulfonamide	88-19-7
	Toluene ethylsulfonamide	8047-99-2
Butane esters	2,2,4-trimetyl-1,3-pentanediole di-isobutyate (TXIB)	6846-50-0
Polyester	No suggestion from industry	-
Epoxyester and epoxydised oils	No suggestion from industry	-
Benzoate	Dipropylene glycol dibenzoate	27138-31-4
	Diethylene glycol dibenzoate	*120-55-8*
	Triethylene glycol dibenzoate	*120-56-9*
Sebacate	Dioctyl sebacate	122-62-3
	Dibutyl sebacate	*109-43-3*

The Danish Product Register has conducted a search on these CAS No.s and a general search to identify which CAS No.s are registered in Denmark as plasticisers.

The result of the general search was that approx. 180 different substances are registered as plasticisers. These were screened with respect to their uses, and only a minority was found to be relevant substitutes for phthalates.

Reduction of the list in Table 4.1 has been performed based on information from the industry, the result of comprehensive information on use patterns from The Danish Product Register, and assessment of the data availability regarding toxicological and ecotoxicological information necessary for the assessment.

4.2.1 Assessed substitutes for phthalates - substances

The plasticisers assessed are those for which most information is expected to be available for the environmental and health assessment and which have a use pattern involving high PVC volume and/or expected high exposure of humans and/or the environment. The substances are listed in Table 4.1.

Table 4.1
Substances used for the environmental and health assessment.

Chemical group	Name of substance	CAS No.	Suggested by DEPA	Identified in Hansen and Havelund (2000)	Plasticiser according to the PR	Known actual application
Adipates	Diethylhexyl adipate	103-23-1	Compound	+	+	Broad application in PVC and non-PVC
Citrates	O-acetyl tributyl citrate	77-90-7	Compound	+	+	PVC, printing ink and concrete products
Phosphates	Di(2-ethylhexyl) phosphate	298-07-7	Compound	-	-	Broad application in PVC
	Tri(2-ethylhexyl) phosphate	78-42-2	Compound	+	+	Paint, glue and adhesive
Mellitates	Tri-2-ethylhexyl trimellitate	3319-31-1	Compound	-	-	Broad application in PVC
Alkylsulphonic acid esters	O-toluene sulfonamide	88-19-7	Group	-	-	Substance proposed by suppliers
Butane esters	2,2,4-trimethyl1,3-pentandioldiisobutyrate (TXIB)	6846-50-0	Group	+	+	Printing ink, paint, glue, adhesive and concrete products.
Polyesters	Polyadipates	-	Group	-	-	Foils, substance proposed by Industry
Epoxy esters and epoxidized oils	Epoxidised soybean oil	8013-07-8	Group	+	+	Printing ink, paint, glue and adhesive
Benzoates	Dipropylene glycol dibenzoate	27138-31-4	Group	+	+	Glue, adhesive
Sebacates	Dioctyl sebacate	122-62-3	Group	+	+	Printing ink and glue

No specific substance to be used as a marker for polyester-substitutes has been identified in PR or from suppliers. The industry has emphasised that these substances may become important and the branch organisation has suggested polyadipate as an example substance. However, no information on health or environmental properties has been identified on this substance or group during the present project.

4.2.2 Assessed substitutes for flexible PVC - materials

Polyethylene (PE) and polyurethane (PU) are both materials which are identified as possible substitutes for flexible PVC in a number of products and they thereby contribute to the overall substitution of phthalates. The two

materials polyurethane and polyethylene substitute the PVC polymer as such and not only the plasticiser additive. Both materials are polymers.

The two alternative materials PE and PUR

In this study low density polyethylene (LDPE) rather than high density polyethylene (HDPE) is selected for the environmental and health assessment, since it is expected that LDPE will substitute plasticised PVC in the main uses in toys and garden hoses.

PU is expected to substitute plasticised PVC in waterproof cloths, shoes, boots and waders, and PUR based on the diphenylmethane-4,4'-diisocyanate (MDI) monomer is selected for the environmental and health assessment.

LDPE and HDPE

Industrial polyethylenes are thermoplastics, which exist in different versions. Low-density versions (LDPE and Linear LDPE) are produced in branched forms in a structure with long and short branches respectively. LDPE is therefore only partly crystalline and the polymer is highly flexible. Principal uses include packaging film, waste bags and soft type plastic bags, tubes, agricultural mulch, wire and cable insulation, squeeze bottles, household items, and toys. LDPE has already substituted flexible PVC in the majority of household packaging products, and the potential for substitution is therefore greater for other product groups like toys.

High density versions (HDPE) are produced in linear forms which allow the polymer chains to pack closely together. This structure results in a dense and highly crystalline material of high strength and moderate stiffness. Principal uses include bottles, pails, bottle caps, packaging, household appliances, and toys. Because of the strength and stiffness HDPE is more commonly used for industrial products compared to household products and consumers in general are more likely to be exposed to LDPE than HDPE. LDPE and HDPE are assumed comparable with regard to effects on environment and health.

HDPE is used for toys of rigid materials, but the proportion of toys manufactured from LDPE compared to HDPE is not known. It has been suggested that the two PE polymers have an equal share of toy market, and it is assumed that LDPE may lead to higher exposures than HDPE.

Polyurethanes

Polyurethanes cover a broad range of synthetic resinous, fibrous, or elastomeric compounds belonging to the family of organic polymers made by the reaction of diisocyanates with other difunctional compounds such as glycols (polyols). Polyurethanes are one of the most versatile of any group of plastics, capable of an almost infinite number of variations in chemistry, structure and application. Polyurethanes can be produced as a foam, in solid form, as an elastomer, coating, adhesive or binder. Foamed polyurethanes form about 90% by weight of the total market for polyurethanes, but there is also a wide range of solid polyurethanes used in many diverse applications.

By itself, the polymerisation reaction produces a solid polyurethane. Polyurethane foams are made by forming gas bubbles in the polymerising mixture, which is achieved by using a blowing agent.

MDI

MDI is one of the most important raw materials to make polyurethane. MDI can be grouped into polymeric MDI, which in the form of foam is being used for several heat protection materials, motor car seats, etc., and monomeric MDI, being used for shoe soles, coating materials, synthetic leather, etc.

Because of the health risks ascribed to monomeric diisocyanates, much attention is paid to the physico-chemical and toxicological properties of the monomer in situations where substitution with a polyurethane is required.

MDI has a particularly low vapour pressure compared to TDI (toluene diisocyanate), HDI (hexamethylene diisocyanate) and IPDI (isophorone diisocyanate) and is under European legislation classified as harmful whereas the other mentioned diisocyanates are classified as toxic. This often makes MDI a better choice where it is technologically feasible.

MDI is already used in the production of PU for waterproof clothes, shoes, boots and waders, application areas, which are suggested for substitution of flexible PVC in the substitution matrix, and is therefore selected to the health and environmental assessment.

4.3 Proposed use pattern for substitutes

The Danish Product Register (PR) has been used to establish an overview of the function of phthalates in chemicals until now. The Register mainly contains information about chemicals and to a lesser extent about materials.

The historical main use of phthalates in Denmark, summarised in Table 4.1, forms the basis for the search for relevant alternatives in the PR.

The most important function of phthalate has until now been plasticising, but besides this function phthalates had have the function of being denaturants in cosmetics (Hoffmann, 1996).

The PR has conducted a search to identify the plasticisers used in selected types of chemical products or materials. The result is illustrated in Table 4.1 for the first 10 that are the substances selected for the assessment. The Polyester was not included due to lack of CAS no.

Table 4.1
The registered use of the selected substances as plasticisers in the selected product groups. Data from the Danish Product Register. The polyester plasticiser (polyadipate) was not included due to lack of CAS no. Materials such as cables, profiles, floor and wall covering are not covered by the PR.

CAS No.	Name	Fillers	Paint and lacquers	Adhesives	Printing inks	Plastic in Concrete	Rubber products	PVC packaging
103-23-1	Di(ethylhexyl) adipate	•	•	•		•	•	
77-90-7	O-acetyl tributyl citrate				•	•		
298-07-7	Di(2-ethylhexyl) phosphate							
78-42-2	Tri(2-ethylhexyl) phosphate	•	•	•		•		
3319-31-1	Tri-2-ethylhexyltrimellitate[a]							
88-19-7	Alkylsulfonic acid ester[a]							
6846-50-0	2,2,4-trimethyl 1,3-pentanediol diisobutyrate (butane ester)	•	•		•	•		•[b]
8013-07-8	Epoxidised soybean oil	•	•	•	•			•
27138-31-4	Dipropylene glycol dibenzoate				•			
122-62-3	Dioctyl sebacate			•				

[a] Not found in the Product Register.
[b] Unclear whether 'plast' is PVC

Not all substances are registered as plasticisers in the selected products. This has to be seen in the light of the fact that the register only contains information about substances classified dangerous to the environment or the health. The result of the search is therefore as mentioned earlier supplemented with industrial information about the development of plasticisers not containing phthalates.

4.3.1 Substitution matrix for the 11 substances in tons

By using the amounts found within the different applications in the substance flow analyse (Hoffmann, 1996) and the proposed %-distribution of the alternatives in Table 4.1, the following "amount-substitution matrix" shown in Table 4.2 within the different applications can be established.

Table 4.1
Substitution matrix for the 11 substances with anticipated share given in %.

Application	Tons phthalates per year (1992)	Diethylhexyl adipate, CAS no. 103-23-1	O-acetyltributylcitrate, CAS no. 77-90-7	Di(2-ethylhexyl)phosphat, CAS no. 298-07-7	Tri(2-ethylhexyl)phosphat, CAS no 78-42-2	Tri-2-ethyl trimellitate, CAS no. 3319-31-1	Toluene sulphonamide, CAS 88-19-7)	2,2,4-trimethyl 1,3-pentanediol diisobutyrate, CAS no. 6846-50-0	Epoxidised soybean oil, CAS no. 8013-07-8	Polyester	Dipropylene glycol dibenzoate, CAS no. 27138-31-4	Dioctyl sebacate, CAS no. 122-62-3	Other substanes and materials	Sum (100%)
Hospital sector	350	25	15	20	20			10					10	100
Packaging	350	15	15	20	10	5		15	10				10	100
Cables	3000	3		25	30	28	1	4	1				8	100
Profiles	80	20		15	15	10		15				15	10	100
Floor and wall covering	1.500	30		20	20	10		10					10	100
Other application of PVC	4.190	20	6	20	20	20		1					13	100
Lacquer and paint	225	10			10			10	30				40	100
Printing ink	270	20	30					10	20			20		100
Adhesive	220	10	5		10				20	15	20	20		100
Filler	400	10	20		10				5	15	40			100
Other applications e.g. in the following products:														
Rubber	50	50											50	100
Concrete	50	10	50		10			5					25	100
Silicone	50												100	100

Note: It is only relevant to ad up the figures horizontal and not vertically because each row describe the substitution within one application. One column represents non-comparable figures.

Based on information from the industry, Table 4.2 represents the best present estimate on substitution of phthalates within different types of products. The dominating amount is for each substance marked in **bold**. The information is primarily based on interviews with industry sources rather than trade bodies, since only little overview information is available.

This best present estimate has to be seen in the light of the situation in which all phthalates in a product are substituted by only one substitute.

The actual substitution five years from now, will presumably not be exactly as illustrated in Table 4.2, but the information indicates in which areas the substances might be used extensively and in which areas the use is expected to be negligible.

It should be emphasised that a large portion of the expected use is placed in "Other applications of PVC" (e.g. toys).

Another scenario is that one substance substitutes the phthalates 100% within an application area (a 'worst worst case').

Table 4.2
Substitution matrix for the 11 substances (in tonnes)

Application	Tons phthalates per year (1992)	Diethylhexyl adipate, CAS no. 103-23-1	O-acetyltributylcitrate, CAS no. 77-90-7	Di(2-ethylhexyl)phosphat, CAS no. 298-07-7	Tri(2-ethylhexyl)phosphat, CAS no 78-42-2	Tri-2-ethyl trimellitate, CAS no. 3319-31-1	Toluene sulphonamide, CAS 88-19-7)	2,2,4-trimethyl 1,3-pentanediol diisobutyrate, CAS no. 6846-50-0	Epoxidised soybean oil, CAS no. 8013-07-8	Polyester	Dipropylene glycol dibenzoate, CAS no. 27138-31-4	Dioctyl sebacate, CAS no. 122-62-3	Other substanes and materials
Hospital sector	350	88	53	70	70			35					35
Packaging	350	53	53	70	35	18		53	35				35
Cables	3,000	90		**750**	**900**	**840**	**30**	120	30				240
Profiles	80	16		12	12	8		12				12	8
Floor and wall cover-ing	1,500	**450**		300	300	150		**150**					150
Other appli-cation of PVC	4,190	838	**251**	838	838	838		42					545
Lacquer and paint	225	23			23			23	**68**				90
Printing ink	270	54	81					27	54			**54**	
Adhesive	220	22	11		22				44	33	44	44	
Filler	400	40	80		40				20	**60**	**160**		
Other appli-cations e.g. in the fol-lowing products:													
Rubber	50	25											25
Concrete	50	5	25		5			3					13
Silicone	50												50
Sum (max.)	10,735	1,704	554	2,040	2,245	1,854	30	465	251	93	204	110	1,190

4.3.2 Substitution matrix for the two materials

In view of the general phase out policy for PVC the substitution of phthalates may obviously take place exchanging the PVC-material by other materials that do not need to be plastified with phthalates. However, PE and PU cannot substitute flexible PVC across-the-board, but as seen in substitution matrix Table 4.1 PE and PU are possible substitutents for flexible PVC in different kinds of products:

- PE will mainly substitute flexible PVC in toys
- PU will mainly substitute flexible PVC in waterproof clothes, shoes, boots and waders.

Using the same procedure as for the 11 substances, but with the 1994-inventory from The Danish Plastics Federation of the consumption of plasticised PVC, a substitution matrix for the PVC-substituting materials can be established as in Table 4.2.

Table 4.1

Substitution matrix for selected flexible PVC products in % of the total amount plasticised PVC (tonnes).

Application	Tons plasticised PVC	Ethylene-vinyl-acetate (EVA)	EPDM rubber	Polyethylene (PE)	Polypropylene (PP)	Cardboard and paper	Leather	Polyurethane (PUR)	Nylon	Neoprene rubber	Natural rubber	Wood	Other	Sum (100%)
Garden hose	450	60	30										10	100
Office supplies	3,500				75	20	5							100
Toys	1,130	30		30	30								10	100
Waterproof clothes	260							80					20	100
Shoes	200						20	50	5		20		5	100
Boots and waders	380							30		5	60		5	100
Sum	5,920	*	*	*	*	*	*	*	*	*	*	*	*	*

*: The vertical sum across different applications of PVC is not relevant to calculate. It is only the horizontal sum within the same application, which is relevant to calculate because it is describing the situation within one specific application and has to add up to 100%.

Table 4.2
Substitution matrix for alternative materials to flexible PVC. The unit is tons.

Application	Tons plasticised PVC	Ethylene-vinyl-acetate (EVA)	EPDM rubber	Polyethylene (PE)	Polypropylene (PP)	Cardboard and paper	Leather	Polyurethane (PUR)	Nylon	Neoprene rubber	Natural rubber	Wood	Other	Sum (100%)
Garden hose	450	270	**135**										45	450
Office supplies	3,500				**2,625**	**700**	**175**							3,500
Toys	1,130	**339**		**339**	339								113	1,130
Waterproof clothes	260							**208**					52	260
Shoes	200						40	100	**10**		40		10	200
Boots and waders	380							114		**19**	**228**		19	380
Sum	5,920	609	135	339	2,964	700	215	422	10	19	268		239	5,920

As for the 11 substances, the information from the industry in Table 4.2 represents the most likely substitution of phthalates within different types of PVC-products. The dominating amount for each material is marked in **bold**.

Again, the substitution five years from now, will presumably not be exactly as illustrated in Table 4.2, but the information indicates in which areas the materials might be used extensively and in which areas the use is expected to be negligible.

The worst case scenario is when one material substitutes the plasticised PVC 100% within an application area.

As seen in Table 4.2, polyethylene is most likely going to substitute 339 tons flexible PVC in toys. With an average concentration of phthalates in soft-PVC toys, similar to 34%, the 339 tons PVC represent 115 tons phthalates.

Polyurethane is, as shown in Table 4.2, the mayor substitute for PVC in waterproof clothes. It is therefore of special interest to undertake an EUSES-calculation on the 208 tons flexible PVC, which may contain up to 100 tons phthalates.

4.4 Assessment of emission and exposure

Data compilation for substitution matrix

The qualitative information from suppliers of phthalates and the alternative substances is based on an assumed complete substitution of phthalate in the mentioned applications in the near future (a five year perspective).

In Table 4.1 and Table 4.1 the qualitative information is transferred to quantitative figures in percent. These figures form a possible scenario for how the complete substitution can take place. It will probably not correspond to the real situation in five years time, but it illustrates where the use of a substance might be extensive and where the use might be negligible. This overview is useful in connection with evaluation of results from calculations in EUSES and in connection with priority of efforts of the environmental regulating authorities.

The 11 substances and the 2 materials in this project are regarded as the main basis for the complete substitution for phthalates.

According to discussion with the organisations listed in the Appendix, the most likely way to substitute phthalates is illustrated in the following substitution matrixes Table 4.1 and Table 4.1.

Substitution matrix for the 11 substances in %

The consumption of phthalates within the relevant applications is based on substance flow analyses covering the situation in 1992 (Hoffmann, 1996). In Table 4.1, the share of 11 substances for the substitution of the phthalates within each application is estimated in %.

According to the Danish Plastics Federation, flexible PVC is not used in packaging, today. The actual consumption of phthalates for this purpose is therefore estimated to be of minor importance.

The first five substances are expected to substitute phthalates directly. The next six are selected as markers for chemical groups from which substitutes are expected to be identified in the near future. Meanwhile the six markers are used to calculate a scenario for substitution of phthalate.

Other substances and materials cover less important substitutions, conducted by other means than the 11 substances. Examples could be substances not covered by the 11 substances in Table 4.2, or new technology in the production of the mentioned products. The new technology could be the use of new materials without the need for plasticising with phthalates.

The point of origin of Table 4.1 is the Danish consumption of phthalates in 1992 shown in Table 4.1 (Hoffmann, 1996). These data are selected because they are the result of a comprehensive survey, and the studies conducted later, confirm the amounts and the indicated development trends within the different applications. For the non-PVC products a decline in the use of phthalates has been identified (Hansen and Havelund, 2000). For the PVC-products the suppliers expect a decline in the near future.

The background for the ratios in Table 4.1 is information gathered in connection with one of the substitution projects initiated by the Danish Environmental Protection Agency. It is the general impression among suppliers and users of phthalates that a complete substitution will be possible for both PVC and non-PVC products. Available substitutes for non-PVC products have been identified earlier (Hansen and Havelund, 2000).

Table 4.1
Estimated use of the substitutes. These volumes are used for consumer exposure

Name of substitute	Expected most relevant application	Expected used amount for the substitution in tons per year
Di(2-ethylhexyl) phosphate, CAS No. 298-07-7	Cables	750
Tri(2-ethylhexyl) phosphate. CAS No. 78-42-2	Cables	900
Tri-2-ethylhexyltrimellitate, CAS No. 3319-31-1	Cables	900
Alkylsulfonic acid ester (toluene sulphonamide, CAS 88-19-7)	Cables	30
Diethylhexyl adipate, CAS No. 103-23-1	Floor and wall covering	450
Butane ester (2,2,4-trimethyl 1,3-pentanedioldiisobutyrate, CAS No 6846-50-0)	Floor and wall covering	150
Epoxidised soybean oil (CAS No. 8013-07-8)	Lacquer and paint	70
o-Acetyl tributyl citrate, CAS No. 77-90-7	Toys	250
Dioctyl sebacate (CAS No. 122-62-3)	Printing ink	50
Polyester	Fillers	60
Dipropylene glycol dibenzoate (CAS No. 27138-31-4	Fillers	160

4.4.1 Considerations regarding specific uses of phthalates/substitutes

Industrial processes

There is no synthesis of phthalates or substitutes for phthalates in Denmark.

The synthesis of phthalates for the Danish market is at the moment mainly conducted in Sweden. The identified substitutes are expected also to be synthesised in countries outside of Denmark.

The main source to emissions and exposures in Denmark is expected to be from formulation of products containing plasticisers such as plasticised PVC, printing inks, adhesives and fillers. For paints and lacquers there is also an emission and exposure from the professional use of the products.

Based on the substitution matrix focus in this investigation has been set on the use of the eleven substances with known potential application the following process:

- Use of di(2-ethylhexyl) phosphate (CAS No. 298-07-7), tri(2-ethylhexyl) phosphate (CAS No. 78-42-2), tri-2-ethylhexyltrimellitate (CAS No. 3319-31-1) and alkylsulfonic acid ester (toluene sulphonamide, CAS No 88-19-7) in the production of cables

- Use of butane ester diethylhexyl adipate (CAS No. 103-23-1), (2,2,4-trimethyl 1,3-pentanediol diisobutyrate, CAS No 6846-50-0) in the production of floor and wall covering

- Professional use of epoxidised soybean oil (CAS No. 8013-07-8) containing lacquer and paint products

- Use of o-acetyl tributyl citrate (CAS No. 77-90-7) and dioctyl sebacate (CAS No. 122-62-3) in the production of printing inks.

- Use of polyester and dipropylene glycol dibenzoate (CAS No. 27138-31-4) in the production of fillers.

In general, uses of the products are regarded as diffuse and as minor sources to emission, but concerning consumer exposure of the 10 substances there are relevant scenarios that are described in Section 5.4.

Human exposure is estimated mainly to take place in connection with:

- Formulation process.

- Uses of the products.

To illustrate the potential human exposure from the 10 well defined substances a calculation in EASE, which is based on the principles in the TDG has been conducted.

EASE calculates a theoretical exposure of humans in the working environment and private consumers.

The input data takes point of origin in the scenarios in Table 4.1, which is assessed to represent the most extensive exposure.

Table 4.1
Exposure scenarios of the 11 substances

	Scenarios	
Name of substance	**Working environment**	**Consumers**
Diethylhexyl adipate (CAS 103-23-1)	Production of follies to floor and wall coverings	Use of floor and wall coverings in bathrooms
o-acetyltributyl citrate (CAS 77-90-7)	Production of printed papers	Daily use of printed papers
Di(2-ethylhexyl)phosphate (CAS 298-07-7)	The well defined step in the production of cables which is the exposure just after the extrusion of cables and before the cooling in water	Contact with cables in a private house
Tri(2-ethyl)phosphate (CAS 78-42-2)	The well defined step in the production of cables which is the exposure just after the extrusion of cables and before the cooling in water	Contact with cables in a private house
Tri-2-ethylhexyltrimellitate (CAS 3319-31-1)	The well defined step in the production of cables which is the exposure just after the extrusion of cables and before the cooling in water	Contact with cables in a private house
o-Toluene sulphonamide (CAS 88-19-7)	The well defined step in the production of cables which is the exposure just after the extrusion of cables and before the cooling in water	Contact with cables in a private house
2,2,4-trimethyl 1,3-pentanediol diisobutyrate (CAS 6846-50-0)	Production of follies to floor and wall coverings	Use of floor and wall coverings in bathrooms
Epoxidised soybean oil (CAS 8016-11-3)	Professional painting in a room without ventilation	Stay in a painted house and conducting painting once a year
Polyester	Production of fillers	Stay in a bathroom with fillers
Dipropylene glycol dibenzoate (CAS 27138-31-4)	Production of fillers	Stay in a bathroom with fillers
Dioctyl Sebacate (CAS 122-62-3)	Production of printing inks	Half an hour interior reading in printed papers

To approach a situation five years from now the exposure calculation in EUSES is therefore conducted for both the most likely situation represented in bold figures and the 100%-scenario.

4.4.2 Worker and consumer exposure

Assessment of the exposure of humans in the working environment and consumers has been conducted using the model *Estimation and Assessment of Substances Exposure Physico-chemical Properties (EASE)*, which is a part of the model *European Union System for the Evaluation of Substances* (EUSES).

Limitations and uncertainties of the EASE

The equations in EASE are intended to provide a simple description of consumer exposure. Most equations give a worst case estimation of exposure, by assuming that all of the compound in the product is at once available for

intake and uptake. Intake and uptake themselves are modelled as simple fractions.

Workers exposure

EASE provides a general-purpose predictive model for exposure assessment in the workplace. The model predicts external exposure only: it does not take into account absorption and bioavailability.

If reliable and representative measured data are available these can be used to overwrite the model results. The general-purpose model is called EASE (Estimation and Assessment of Substance Exposure) which is described in details in Section 2.2 of the TGD.

EASE was specifically developed for the purpose of modelling inhalation and dermal workplace exposure across a wide range of circumstances.

EASE is an analogue model, i.e. it is based on measured data which are assigned to specific scenarios. The user can build scenarios by choosing between several options for each of the following variables: physical properties during processing (tendency to become airborne, potential for dermal contact), use pattern and pattern of control. Numerical ranges have been assigned using measured data contained within the UK National Exposure Database for inhalation exposure, and experimental data and expert judgement for dermal exposure.

The data used to assign ranges within the model are all 8-hour time weighted averages and the numbers generated by the model are only valid when the exposures being assessed can be related to such averages.

The output of EASE is numerical ranges of concentrations or ppm. These are converted from ppm to $kg.m^{-3}$ and can be used as input for risk characterisation in which the exposure estimates are compared to the results of the human effects assessment.

Consumer-exposure

The consumer, i.e. a member of the general public who may be of any age, either sex, and in any stage of health may be exposed to chemical substances by using consumer products.

A consumer product is one, which can be purchased from retail outlets by members of the general public and may be the substance itself, or a preparation, or an article containing the substance.

The EASE equations for consumer exposure can be used to estimate external exposure substances used as or in consumer products. Absorption or bioavailability is not taken into account by the equations implemented in EASE.

The focus in EASE is on substances used indoors for a relatively short period of time per event (such as e.g. a carrier/solvent in a cosmetic formulation; a powder detergent).

The equations in the model apply to both volatile substances and airborne particulates. It is assumed the substance is released as a vapour, gas, or airborne particulates, and the room is filled immediately and homogeneously with the substance. Ventilation of the room is assumed to be absent.

The equations can also be adapted to estimate exposure arising from 'reasonably foreseeable misuse', i.e. when products are not used according to the instructions, but as if they were other, allied products.

To adapt the equations, the values for the parameters used in the equations are changed to reflect values foreseen in "reasonably foreseeable misuse". For example, the volume of product or the area of application is set to a different value, reflecting reasonable foreseeable misuse.

If a substance is released relatively slowly from a solid or liquid matrix (e.g. solvent in paint, plasticiser or monomer in a polymer, fragrance in furniture polish), the equation in EASE acts as a worst case estimation, estimating the maximum possible concentration.

Dermal

The calculation in EASE has in this investigation been operating with two scenarios concerning dermal exposure: A and B.

Dermal A: a substance contained in a medium. This dermal scenario also applies to

- a non-volatile substance in a medium used without further dilution (set dilution D=1), and
- a non-volatile substance in a volatile medium.

The assumption behind the equations in the calculations is that all of the substance on the skin is potentially available for uptake. This is the case when the medium is well mixed or only present as a thin film on the skin. The dermal equations apply for:

- a non-volatile substance in a diluted product,
- a non-volatile substance in a medium used without further dilution, and,
- a non-volatile substance in a volatile medium.

Dermal B: a non-volatile substance migrating from an article (e.g. dyed clothing, residual fabric conditioner, dyestuff/newsprint from paper).

The assumption behind the equation is that only part of the substance will migrate from the article (e.g. dyed clothing, residual fabric conditioner, dyestuff/newsprint from paper) and contact the skin. The migration is assumed to be slow enough to be represented by a constant migration rate multiplied by the time of contact.

The exposure calculation will involve estimating the amount of substance which will migrate from the area of the article in contact with skin during the time of contact. Dyestuff amounts in fabrics and paper are usually given as weight of product per unit area (e.g. mg/m^2).

Oral

The calculation concerning oral exposure has also been operating with two scenarios: A and B.

Oral A: a substance in a product unintentionally swallowed during normal use (e.g. toothpaste).

The exposure equations may also be used to estimate exposures arising from ingestion of the non-respirable fraction of inhaled airborne particulates. The equations may also be used to estimate exposures arising from ingestion of the non-respirable fraction of inhaled airborne particulates.

Oral B: a substance migrating from an article into food or drink (e.g. plastic film, plastic-coated cups/plates).

It is assumed that the substance in a layer of thickness of article (e.g. plastic film, plastic-coated cups/plates) in contact with the food will migrate to the food. The migration rate is assumed to be constant, and the migration rate multiplied by the contact duration is the fraction of substance that is migrated to the food. The equation can be used to give a conservative estimate of substance uptake by a defined volume of food. The value of the migration rate will be influenced by the type of food (e.g. fatty/dry/moist), the period of exposure and the temperature at which it occurs. Consumer exposure level will also be influenced by the proportion of contaminated food eaten.

Use pattern scenarios

Based contacts to the Danish industry and the substance flow analyse (Hoffmann, 1996) relevant scenarios has been identified and are described in section 4.3.

The background for choosing scenarios is the most likely way of substitution described by industrial actors and rendered in the substitution matrix in Table 4.1. Within the substitution matrix the application representing the largest estimated consumption of each substitute is selected as the most relevant scenario. This application is marked in bold figures in the substitution matrix.

The input data for the calculation are the substitution matrix and scenarios with the largest estimated consumption substitute for phthalate plasticisers.

With point of origin in the substitution matrix the substances are distributed in the following most relevant application areas.

Plasticisers in the "Cables"-application are expected to be:

- Di(2-ethylhexyl) phosphate, CAS No. 298-07-7
- Tri(2-ethylhexyl) phosphate. CAS No. 78-42-2
- Tri-2-ethylhexyltrimellitate, CAS No. 3319-31-1
- Alkylsulfonic acid ester (o-toluene sulphonamide, CAS No 88-19-7).

For the production of "floor and wall covering" the following plasticisers are chosen:

- Diethylhexyl adipate, CAS No. 103-23-1
- Butane ester (2,2,4-trimethyl 1,3-pentanediol diisobutyrate, CAS No 6846-50-0).

Concerning the production of lacquer and paint the focus is on:

- Epoxidised soybean oil (CAS No. 8013-07-8).

In connection with printing ink the relevant substances are estimated as:

- O-acetyl tributyl citrate, CAS No. 77-90-7
- Dioctyl sebacate (CAS No. 122-62-3).

The production of "fillers" is assumed to include:

- Polyester
- Dipropylene glycol dibenzoate (CAS No. 27138-31-4).

The scenarios in EASE for the consumer exposure are based on the amounts for these uses and the exposure characteristics for the application.

4.4.3 Exposure in environment

Substance parameters

For each substance the required input parameters molecular weight, octanol-water partition coefficient, water solubility, vapour pressure and physical state were fed to the model in accordance with the data search and evaluation.

Two types of assessments were performed for each substance substituting phthalates. One scenario simulates the best educated guess for the future share that this particular substance would gain in the market based on interviews with the industry. The second assessment simulates the hypothetical situation where only one of the alternatives (100% substitution case) substitutes the entire tonnage of phthalates.

In the 100% substitution case it is chosen to base the estimates on the most recent inventory of the phthalates in PVC and use the sum used in 1992 (10,735 tons). In various applications substitutes may be used in different volumes than the phthalates – if 1 kg new substance can substitute 2 kg phthalate or *vice versa*. Since the available information on this is very incomplete it has been decided not to try to include such information in the calculations.

The physical parameters of some of the compounds are out of the advised range in which EUSES operates. In the cases where the physical parameters are out of the pre-set range (e.g. $\log P_{ow} > 6$) or unknown as melting and boiling point sometimes are, it has been chosen to use the nearest maximum or minimum value as suggested in EU TDG or use a worst case approach.

All results are presented in the report with two significant digits rounded off from the EUSES calculations with three significant digits (given in appendix).

The assessment of emission to the environment and exposure of man and biota from environmental concentrations of phthalate alternatives are based on the procedures outlined in the EU TGD (EU Commission 1996). The actual concentrations are calculated by using the PC program EUSES (European Chemicals Bureau 1996), which is designed to provide decision support for the evaluation of the risks of substances to man and the environment based directly on the EU TGD.

In the present evaluation EUSES is operated in three of the possible five modes. Parameters are entered for:

I. Environmental assessment,

II. Predators exposed via the environment and

III. Humans exposed via the environment.

EUSES will calculate concentrations and doses for the assessment on three spatial scales: the local (point source), the regional (small and densely inhabited country) and the continental (Europe). The default regional scale has been changed to suit Danish conditions (see below). The local and continental scenarios are included in the calculations, but no specific values have been entered.

The EUSES program calculates environmental exposure based on 1) a physical scale where the use and emission takes place, 2) the use and emission pattern of the substance and 3) on substance specific parameters. The specific parameters for each substance are provided for each exposure estimation. To assist the comparison between substances the physical dimensions of the scenario and the overall industrial use and emission pattern has been set identical for all substances.

Use and emission scenarios

The use and emission scenarios rely on the database of emission scenario documents for a number of industrial uses included in EUSES. The following settings have been used to represent the primary use of phthalate alternatives:

Emission input data	No.	Name
Industry category	11	Polymers industry
Use category	47	Softeners
Main category (production)	III	Multi-purpose equipment
Main category (formulation)	III	Multi-purpose equipment
Main category (processing)	IV	Wide dispersive use

Danish regional scenario

The physical dimensions of the regional scenario have been set at values representative for Denmark, those changed are shown in Table 4.1 (a complete list of parameters can be found in the Appendix). The values were taken from the evaluation of the SimpleBox Model for Danish conditions (Miljøstyrelsen 1995).

Table 4.1
Parameters of the EUSES model, which were adapted to Danish conditions

Parameter	Value	Units
Fraction of EU production volume for region	0.05	[-]
Fraction connected to sewer systems	0.9	[-]
Environmental temperature	7.7	[^{o}C]
Volume fraction water in soil	0.4	[m3.m-3]
Weight fraction of organic carbon in soil	0.025	[kg.kg-1]
Number of inhabitants of region	5.30E+06	[eq]
Wind speed in the system	5	[m.s-1]
Area of regional system	4.30E+04	[km2]
Area fraction of water of the regional system	0.011	[-]
Area fraction of natural soil	0.332	[-]
Area fraction of agricultural soil	0.647	[-]
Area fraction of industrial/urban soil	0.01	[-]
Suspended solids concentration of regional system	17.7	[mg.l-1]
Net sedimentation rate	8.22	[mm.yr-1]
Average annual precipitation	735	[mm.yr-1]
Fraction of rain water infiltrating soil	0.46	[-]
Calculate dilution from river flow rate	No	
Mixing depth of grassland soil	0.05	[m]
Mixing depth agricultural soil	0.2	[m]

4.4.4 Migration potential

A key parameter in comparing various plasticisers is their potential for migrating out of the PVC polymer. Only few data has been identified on migration potential for the substitutes. The information on migration potential will be used in the expert assessment process, but is not used in the exposure calculation model.

To determine the total migration potential various reference methods are used which all are available as CEN standards (ENV 1186-1 – ENV 1186-12). Several new standards in this area are in preparation.

In general the methods are divided in two categories: Migration from plastic to an oily extractant and migration from plastic to an aqueous solution.

To determine the total migration potential using the two groups of methods either a double sided test (total submergence of plastic piece) or a single sided test (using a migration cell or by incorporating the plastic piece into a bag) is performed.

The total migration potential is determined as the difference in weight before and after extraction or as weight of the evaporation residue of the extractant.

The 3 commonly water based extractants are distilled water, 3% acetic acid and 10 % ethanol. Since most plasticisers are lipophilic it is most relevant to express the migration as migration from plastic to fat containing food. As fat simulator olive oil is the commonly used.

The amount of plasticiser extracted is extractant dependent and usually the extraction time of olive oil and 95% ethanol is 10 days at 40 °C and for iso-octane 2 days at 20 °C.

The difference in extraction time is due the extraction power of each extractant and the ability of the extractant to make the plastic swell. When the plastic swells the dept of the layer in contact with the extractant increases and the amount of platisicer extracted increases.

The extraction power of the extractant types depends on the plastic type that is investigated, but usually, when considering plastics that contains lipophilic plasticisers the order extraction power is: isooctane > olive oil > ethanol.

5 Health and environmental assessment for compounds

Datasheets for the assessed substances appear in appendix and provide detailed information. Here, the key data are presented and used for the assessment. The results of the exposure and dose calculations performed with EUSES are presented in tables. The selected scenarios cover consumer exposure, exposure in the workplace and exposure from the environment. In the tables presenting regional concentrations $Surface_t$ and $Surface_d$ denotes concentration of the substance in the total water and in the dissolved phase, respectively.

The toxicity data selected for the assessment of human toxicity are primarily observations in humans (where available) and test results from standard animal tests used in classification of chemical substances in accordance with the EU Substance Directive (EEC 1967). In presenting human toxicity data the tables contain what is considered the core data regarding the effects. These and additional data can be found in the appendix. The information used for the evaluation is discussed in the text.

Acute toxicity, irritation, sensitivity, subchronic toxicity and long-term effects are discussed where possible. If a NOAEL or a LOAEL is established, this estimate is included in the assessment and also discussed in relation to the selected exposure scenarios. If an ADI-value is established for the substances, the calculated exposure scenarios are discussed in the light of this value taking all possible exposure routes and situations into consideration.

The ecotoxicity data have been selected with preference to results based on the standard ecotoxicity test methods for algae, crustaceans and fish, as recommended in Pedersen et al. (1995) and used in the environmental hazard classification process. Thus, in the case where the acute test is the 72 hours algae test (IC_{50}), 48 hours crustacean test (EC_{50}), and 96 hours fish test (LC_{50}), the result in mg/l is presented without further explanation. If the result comes from a test of other duration or endpoint etc, the deviation will be stated. For biodegradation the standard test is the 28 days of readily or inherent degradability. Unless it is stated otherwise, all BCF data are measured, and values above 100 are considered indicative of bioaccumulative properties.

5.1 Di(ethylhexyl) adipate; 103-23-1

Adipates are (as sebacates and azalates) diesters of aliphatic dicarboxylic acids and are produced with varying alcohol groups.

The adipates are classified as low temperature plasticisers. The compounds of this group are all relatively sensitive to water.

5.1.1 Use, emission and exposure

Physical-chemical properties

The measured solubility of di(ethylhexyl) adipate (DEHA) in water at 20-22 ^oC ranges from 0.8 mg/l to <100 mg/l, which places this substance in the group of the moderately soluble substances investigated in this assessment.

DEHA has a measured vapour pressure at 20-25 ^{o}C ranging from 8.5×10^{-7} to 2.6 mm Hg. A value of 8.5 1×10^{-5} is used for the assessment. The magnitude of this parameter places DEHA in the group of investigated substances that possesses a moderate to low vapour pressure.

The estimated $LogP_{ow}$ values of 4.2 to 8.1 (BUA 1996a) and one measured value of > 6.1 (HSDB 2000) indicates that this substance is lipophilic. The default maximum value of 6 was used for the EUSES estimation.

Migration

The measured reduced migration potential (household cling to olive oil) of 2.6-41.3 mg/dm^2 indicates that DEHA have the potential of migrating from the PVC phase to a fatty phase in contact with the PVC (Petersen, Breindahl, 1998). In the same study other plasticisers such as dibutyl phthalate (DBP) were shown to possess lower migration potentials (0.2-1.1 mg/dm^2) relative to DEHP.

Use pattern for compound

DEHA is the dominant compound in the group of adipates, and is mostly used in thin clear household cling intended for food wrapping.

As seen in Table 4.2 DEHA is expected to be widely used in the near future to in various areas such as in products for the hospital sector and in packaging. DEHA is also expected to be used in products such as printing inks, adhesives, fillers and products now containing various amounts of PVC-plastic.

Exposure in work place

The EASE calculation focuses on the production of floor and wall coverings.

The following assumptions are made with regard to the process:

- a press is used for production
- the temperature is 200 °C
- a required legal exhaust ventilation is in place.

Possible main exposure routes in the workplace:

- inhalation of vapours and aerosols
- skin contact from contact with aerosols is considered to be insignificant.

Based on this scenario, the EASE calculation gives the following estimates of exposures shown in Table 5.1.

Table 5.1
Estimated values of DEHA in the working environment according to the EASE calculation.

Route of exposure	EASE value	Unit
Vapour concentration in air for workers	10-50	ppm
Vapour concentration in air for workers	154-771	mg/m^3
Potential dermal uptake for workers	0	mg/kg/day

Consumer exposure

The direct exposure from floor and wall coverings is estimated by an EASE calculation and the results are shown in Table 5.2.

Table 5.2
The estimated potential daily intake of DEHA by consumers according to the EASE calculation

Route of exposure	Daily intake in mg/kg bw/day	Ratio to the ADI (0.3 mg/kg bw/d)
Inhalatory intake	4.34×10^{-10}	1.45×10^{-7}
Dermal uptake	4.56×10^{-4}	1.52×10^{-3}
Oral intake	0	0
Total chronic uptake via different routes	4.56×10^{-4}	0.0015
Total acute uptake via different routes	0	0

The broad application of DEHA means that the total exposure of consumers from all possible sources will be higher than the values indicated in Table 5.2.

The ability of DEHA to migrate from plasticised products e.g. packing materials to more lipophilic environments leads to the conclusion that the potential exposure of consumers may be even larger, if DEHA is going to substitute phthalates as described in the substitution matrixes.

Haemodialysis

Haemodialysis is selected as a second scenario for consumer exposure to DEHA. This is the application where high exposure is identified for bis(2-ethyl-hexyl)phthalate (DEHP) in KemI (2000).

In this scenario focussing on the use of DEHA in plasticised tubing for haemodialysis, the concentration of DEHA in blood is estimated at 6.0 - 8.4 mg/l. This figure is reached using the following data and assumptions:

Re-circulation of PVC-tubing with humane plasma for five hours resulted in extraction of 4.2 mg DEHA into a volume of 500-700 ml and thereby a concentration of 6.0 - 8.4 mg/l in blood. If this amount of DEHA is distributed to the full blood volume (5 l), the resulting concentration would be 0.84 mg/l. This figure is probably lower than what would be expected from a real dialysis situation, where the full blood volume is re-circulated. A more realistic value is expected to be in the range of 0.84 - 8.4 mg/l blood after a single treatment. This corresponds to 16.8 - 168 µg/kg bw for a 50 kg person per treatment session. Assuming three treatments per week this will correspond to an average daily exposure of 2.9 - 72 µg/kg bw/day.

Milk tubes

A special scenario has been set up for the use of DEHA in tubes used when stripping cows.

According to (Jensen, 2000) plasticised tubes are only used for transporting the milk 1 meter from the cow to the milk carrier system in the stable. This tube is estimated to have a internal diameter on 1.6 cm and an external on 1.8 cm and a length equal to 1 meter (Jepsen, 2000). This leads to a volume of the tube equal to = 0.214 dm^3 = 0.214 l. The density of the tube is esti-

mated to 1 kg/l leading to a weight equal to 0.214 kg. The lifetime is assumed to be one year.

The content of DEHA is 7-40% and this is estimated to migrate from the tube 100% within the lifetime. The amount of DEHPA migrating from 1 metre of tubing is 85,000 mg pr year.

It is assumed that the tube is used to strip 25 cows pr. year. One cow produces 6,836 kg milk pr. year with a density of 1 kg/l.

In this scenario the minimum concentration of DEHA in the milk will be 0.088 mg/l and the maximum will be 0.50 mg/l. If a child weighing 10 kg drinks 1 litre of milk per day, the average daily intake from this source would be a maximum of 0.05 mg/kg bw/day.

Environmental exposure of human

The amount established in the 'Usage' section is used to calculate exposure for a number of environmental compartments by EU TGD/EUSES. The dose is almost completely derived from consumption of root crops. This is due to the extraordinary high $LogP_{ow}$ of DEHA leading to accumulation in agricultural soil when sludge is used for soil amendment. No measured data are available for accumulation in plants.

Table 5.3
The estimated human doses of DEHA through intake of water, fish, leaf of crops, roots of crops, meat, milk and air.

DEHA		Estimation (~1,700t)	Worst case (10,700t)
		mg/kg/d	mg/kg/d
Drinking water		6×10^{-7}	4×10^{-6}
Fish	BCF measured	5×10^{-7}	3×10^{-6}
Plants	Leaf crops	0.00005	0.00033
	Root crops	0.007	0.047
Meat		0.00011	0.00072
Milk		0.00007	0.00042
Air		1×10^{-7}	6×10^{-7}
Total regional		0.0076	0.0481

Exposure in the environment

The estimated concentration levels of DEHA reflect the low solubility in aqueous solutions combined with a high $LogP_{ow}$ and a resulting association with particles (sediment and soils).

Table 5.4
The estimated regional concentrations of DEHA in water, soil and air.

Compartment	Aquatic			Terrestrial				Air
DEHA	$Surface_t$	$Surface_d$	Sediment	Natural	Agricul-tural	Porewa-ter of agri. soil.	Industrial	
	mg/l	mg/l	mg/kg	mg/kg	mg/kg	mg/l	mg/kg	mg/m^3
Estimation (~1,700 t)	0.000022	0.00001	0.24	0.0023	0.24	0.00002	1.9	4.5×10^{-5}
Worst case	0.00014	0.00007	1.5	0.015	1.6	0.00013	12	2.9×10^{-6}

Secondary poisoning

The accumulated concentration in fish, roots of plants, meat and milk reflects the estimated high lipophilicity of DEHA.

Table 5.5
The estimated regional concentrations of DEHA in fish, plants, meat and milk.

Articles of food	Wet fish		Plants			Meat	Milk
DEHA	Estimate	Measured	Roots	Leaves	Grass		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kgww	mg/kgww	mg/kgww
Estimation (~1,700 t)	0.48	2.8×10^{-4}	1.3	0.003	0.003	0.03	0.008
Worst case (10,700 t)	3.02	1.8×10^{-3}	8.5	0.019	0.019	0.17	0.053

5.1.2 Health assessment

The key toxicity data for the assessment of DEHA are presented in Table 5.1.

Table 5.1
Selected toxicity data on DEHA.

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Acute oral toxicity	Rat	N.D.		LD_{50}=7,392 mg/kg bw	1a, 5, 9
Acute inhalation toxicity	Rat	N.D.	900 mg/m^3 / 4h	No effects	11
Acute dermal toxicity	Rabbit	N.D.		LD_{50}=8,410 mg/kg bw	1a, 4, 5, 10
Acute toxicity, other routes	Rabbit	N.D.		$LD_{50,\ i.v.}$=540 mg/kg bw	1a, 4, 5, 12
	Rat	N.D.		$LD_{50,\ i.v.}$=900 mg/kg bw	1a, 4, 5
	Mouse	N.D.		$LD_{50,\ i.p.}$=150 mg/kg bw	1a
Irritation - skin	Rabbit (albino)	Draize test	462 mg/6.5 cm^2 24 hour	Slightly irritating (average of 0.83 points out of 8)	5
- eye	Rabbit	N.D.	462 mg (0.5 ml) 24 hours	Small foci with necrotic tissue	5
	Rabbit	N.D.	0.1 ml (92.4 mg)	Not irritating	5
Sensitisation	Guinea pig (♂)	Draize	i.c.:1. day: 0.1% (0.5 ml) + 3×0.1% (0.1ml) for 3 weeks, Challenge: 0.1% (0.5ml)	No effect	5, 16
Repeated dose toxicity	Mouse (B6C3F1)	N.D	240-3750 mg/kg/day; 13 weeks	Reduced bodyweight gain at 465 mg/kg bw	1a, 5, 7
	Mouse (B6C3F1)	Investigation of liver peroxisome proliferation (oral)	0, 32, 325, 3322, 6370 mg/kg/day; 21 days	Reduced bodyweight gain, increased liver weight and peroxisome numbers in liver cells. NOAEL=325 mg/kg bw	1b
	Rat (strain unknown)	N.D. (oral)	610-4760 mg/kg/day, 90 days	Reduced bodyweight gain, changes in liver and kidney weight. Adverse effects on liver, kidney, spleen and testes. NOAEL=610 mg/kg bw	1a, 5, 6
	Rat (strain unknown)	N.D. (oral)	700 and 1,500 mg/kg/day; 2 years	Reduced bodyweight gain, NOAEL=700 mg/kg/day, LOAEL= 1,500 mg/kg/day	3
	Rat (Fisher 344)	Investigation of liver peroxisome proliferation (oral)	11, 122, 1177, 2275 mg/kg/day; up to 21 days	Reduced bodyweight gain, increased liver weight and peroxisome numbers in liver cells. NOAEL=122 mg/kgbw	1b

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Genetic toxicity	*Salmonella typhimurium*	Ames test, +/-	0.025-10 mg/plate	Not mutagenic	2, 3, 5, 13
	Mouse	Dominant lethal mutation study	0, 0.45, 0.9, 4.6, 9.2 g/kg bw i.p.	LOAEL=450 mg/kg bw	3, 5, 8
	Human lymphocytes	OECD 473	10, 50, 100 µg/ml	Negative	1a, 5, 14
	CHO cells	In vitro mammalian cell gene mutation test, +/-	<400 µg/ml	Weak positive without S9	1a, 5, 15
Reproductive / developmental toxicity	Rat, Alpk:APfSD	Fertility study, OECD 415	28, 170 1,080 mg/kg/day; 10 weeks	NOAEL, parental = 170 mg/kg bw/day NOAEL, F0 = 170 mg/kg bw/day	16
	Rat, Alpk:APfSD	Developmental, OECD 414	28, 170 1,080 mg/kg/day; 22 days	NOAEL, foetotoxicity = 28 mg/kg bw/day NOAEL, parental = 170 mg/kg bw/day, LOAEL = 1080 mg/kg bw/day.	3, 5
Carcinogencity	Mouse (B6C3F1)	N.D.	1,800 and 3,750 mg/kg bw/day, 103 weeks	Dose-dependent incidence of liver tumours (adenomas and carcinomas). Significantly higher no. of ♀ with carcinomas.	1a, 2, 5, 7
	Rat (Fisher 344)	N.D.	600 and 1,250 mg/kg bw/day, 103 weeks	No substance related effect.	1a, 5, 7
	Rat (F-344) and mouse (B6C3F1)	N.D.	2.5 g/kg bw/day Duration unknown	Higher sensitivity for F-344 rats than B6C3F1 mice to peroxisome proliferation.	2
Experience with human exposure	Human	Inhalation	11.7 - 14.6 µg/m^3	More pronounced reactions in humans with allergy case history	1a, 5
	Human	Patch-test	Neat DEHA, booster after 14 days	No irritation or sensitisation	5

References: 1a) European Commission Joint Research Centre (1996), 1b) European Commission Joint Research Centre (2000), 2) HSDB (2000), 3) IRIS (2000) 4) NTP (2000), 5) BUA (1996a), 6) Smyth et al. (1951), 7) DHHS/NTP (1981), 8) Singh et al. (1975), 9) Kolmar Res. Ctr. (1967), 10) Union Carbide quoted in Sax, N.J. and Lewis, R.J. Jr. (eds); (1989), 11) Vandervort and Brooks (1977), 12) Edgewood Arsenal (1954), 13) Zeiger et al. (1982), 14) ICI PLC (1989b), 15) Galloway et al (1987), 16) SIDS dossier (1998).

Observations in humans

Most of the identified observations in humans are related to cosmetic products with a certain content of DEHA, but without available information regarding the other constituents. These observations are therefore not used in the evaluation. Exposure to neat DEHA did not cause significant irritation or sensitisation reactions (BUA, 1996a).

In the meatpacking industry, 685 workers were investigated. The average DEHA concentration in the rooms was 11.7 µg/m^3 to 14.6 µg/m^3. Workers with asthma or allergy seemed to get more pronounced reactions. No further details are available (BUA, 1996a).

Acute toxicity

DEHA shows very little acute toxicity in animal studies. Administered orally, the lowest observed LD_{50} in rat was 7,392 mg/kg bw. LD_{50} values (oral) in rat have been reported up to 45,000 mg/kg. Dermal LD_{50}'s have been found in the range of 8,410 to 15,100 mg/kg in the rabbit (European Commission Joint Research Centre, 1996).

When administered intravenously, DEHA is slightly more toxic, with a LD_{50} to rat of 900 mg/kg bw and a LD_{50} to rabbit of 540 mg/kg bw (BUA, 1996a).

Based on the available limited data, DEHA does not show effects when inhaled for a short period of time.

Irritation

DEHA has been reported to be non-irritating or slightly irritating to the skin and eyes of rabbits in a number of different studies. Slight irritation was observed in a study where 0.5 ml / 462 mg DEHA was applied to rabbit skin for 24 hours. 462 mg of test substance instilled in the in rabbit eye produced small foci with necrotism. Detailed information about the test conditions and results are not available (BUA, 1996a).

Sensitisation

DEHA did not produce signs of a sensitising potential in a Draize test in guinea pigs (BUA, 1996a).

Repeated dose toxicity

A number of different repeated dose toxicity studies have shown that DEHA can produce dose dependent changes in body and organ weights and in biochemical parameters as well as changes indicative of peroxisome proliferation. A precise determination of a NOAEL for DEHA for repeated dose toxicity is not available. A NOAEL in rats of 610 mg/kg bw/day was observed in a 13 week feeding study (Smyth et al., 1951). In rats a NOAEL of 122 mg/kg bw/day for peroxisomal proliferation was identified in 21 day feeding study, and in a similar study in mice the NOAEL was identified at 325 mg/kg bw/day (European Commission Joint Research centre, 2000). No details are available in the reviewed literature. The Scientific Committee for Food has assigned a NOAEL for DEHA in the rat, as measured by biochemical parameters and electronmicroscopic analysis of peroxisome proliferation, at approximately 100 mg/kg bw/day (CSTEE, 1999).

Genetic toxicity

The mutagenicity of DEHA is weak in the available studies and only observed in mice. Most significant was an observed dominant lethal effect in male mice, here the LOAEL was 450 mg/kg bw (Singh et al., 1975).

Long term toxicity

According to IARC, DEHA is not classifiable as a human carcinogen. It is grouped as a category 3 carcinogen: Limited evidence of carcinogenicity in animals (IARC, 2000).

In the available literature DEHA has been shown to cause a significantly increased incidence of liver tumours in female mice and a non-significantly increased incidence in male mice (a 2-year study), and that changes in liver biochemistry has been observed in rats (among other changes in cytochrome P450) (European Commission Joint Research centre, 1996). Liver tumours are proposed to be induced by peroxisome proliferation through a mechanism which involves hormone receptors expressed at a much lower level in human liver than in mice (CSTEE, 1999).

Reproductive and developmental toxicity is investigated in a number of studies. In the available literature the lowest maternal toxicity was observed at a level of 170 mg/kg bw/day in rats. A NOAEL of 28 mg/kg bw/day for foetal toxicity resulting in skeletal variations, kinked or dilated ureters was established in a rat study following the OECD 414 guideline (BUA, 1996a). The Scientific Committee for Food has established a NOAEL for foetotoxicity at 30 mg/kg bw/day (CSTEE 1999).

NOAEL/LOAEL

The lowest reported NOAEL in the reviewed literature is this NOAEL of 28 mg/kg bw/day for foetal toxicity in rats, which must be considered the most sensitive effect. The most critical effect of the structural analogue DEHP, namely testicular toxicity (KemI, 2000), has not been addressed for DEHA in the reviewed literature.

Toxicokinetics

The main metabolite in human blood is 2-ethylhexanoic acid. Its elimination half time was found to be 1.65 hrs. In urine the observed metabolites were 2-ethylhexanoic acid (8.6%), 2-ethyl-5-hydrohexanoic acid (2.6%) 2-ethyl-1,6-hexanedoic acid (0.7%), 2-ethyl-5-ketohexanoic acid (0.2%) and 2-ethylhexanol (0.1%). The elimination half time was approx. 1.5 hours. After 36 hrs no metabolites were detected in the urine (HSDB, 2000).

Summation/Conclusion

Based on the available literature DEHA has been shown be of low acute toxicity and to cause slight irritation to rabbit skin and eyes in some studies. DEHA has not shown a skin sensitisation potential in the reviewed literature.

In reproductive toxicity studies DEHA has shown to produce foetal toxicity in rats. A NOAEL of 28 mg/kg bw /day was established (BUA, 1996).

DEHA is reported to cause liver tumours in mice. CSTEE (1999) proposes that liver tumours are induced by peroxisome proliferation through a mechanism which involves hormone receptors expressed at a much lower level in human liver than in mice.

According to IARC, DEHA is not classifiable as a human carcinogen and it is classified as a category 3 carcinogen: Limited evidence of carcinogenicity in animals. This conclusion has been drawn by a working group re-evaluating the evidence for carcinogenicity for 16 industrial chemicals, reported in the IARC Monograph, Volume 77. DEHA causes peroxisome proliferation in the liver in mice and rats, but evidence that this compound is carcinogenic in experimental animals is less than sufficient. Considerations of mechanism or mode of action of DEHA therefore played no role in the classification by the working group. In relation to the structural analogue, DEHP, the working group has concluded that the mechanism by which DEHP increases the incidence of hepatocellular tumours in rats and mice is not relevant to humans. DEHP produces liver tumours in rats and mice by a non-DNA-reactive mechanism involving peroxisome proliferation, which has not been demonstrated in human hepatocyte cultures or exposed non-human primates. (IARC, 2000).

The mutagenicity of DEHA is weak.

An ADI on 0.3 mg/kg bw/day for DEHA has been estimated by the EU´s Scientific Committee for Food (SCF, 2000). This value is far above the results from the EASE calculation. It is therefor estimated that the selected scenario will not contribute to the daily human intake of DEHA in a significant amount.

Critical effect

The identified critical effect of DEHA in a developmental study is foetotoxicity. The established NOAEL is 28 mg/kg bw/day.

Classification

Based on the available data, the only observed effect which could result in classification according to the criteria in the EU Substance directive (EEC 1967) is foetal toxicity in rats. This would, however, require more detailed information.

Exposure versus toxicity

A comparison between the calculated exposure of consumers and the available toxicological information about DEHA indicates that the selected exposure scenario regarding floor and wall coverings represents a minor risk to human health. DEHA is however widely used, and when other possible sources of exposure are taken into consideration, the total load of DEHA may reach the same order of magnitude as the established ADI.

Comparing the estimated daily exposure to DEHA from haemodialysis to estimated daily exposure in a similar scenario for DEHP shows that the average daily exposure of 2.9 - 72 μg/kg bw/day for DEHA is 50 - 1000 times lower than for DEHP, which is considered more toxic than DEHA. For comparison the lowest LD_{50} for DEHP administered intravenously to rats and reported in the reviewed literature is 250 mg/kg bw. It should be mentioned that this study is reported to be inappropriate for a risk assessment due to poor design and/or reporting (KemI 2000). The LD_{50} for DEHA administered intravenously to rats and reported in the reviewed literature is 900 mg/kg bw and 540 mg/kg bw in rabbits. The NOAEL for the critical foetotoxic effect of DEHA to rats is approximately 0.4×10^3 - 10×10^3 times higher than the estimated average daily exposure from haemodialysis.

Possible adverse effects have been observed in humans following inhalation of concentrations of 11.7 μg/m^3 to 14.6 μg/m^3. As the selected workplace scenario in EASE results in concentration levels 10^4 times bigger, similar or more severe effects can be expected, even though the EASE calculation must be considered rather conservative.

Based on the available data the milk tube scenario may indicate that if a child with a weight of 10 kg drinks 1 l of milk pr. day the maximum dose will be 0.05 mg/kg bw. As the ADI is 0.3 mg/kg/bw, the maximum dose is 17% of the ADI.

5.1.3 Environmental assessment

Generally, data on the environmental effects from DEHA are available, especially from the acute aquatic test systems. In the following the most sensitive data is presented.

Table 5.1
Ecotoxicity and fate data on DEHA

	Aquatic (mg/l)			Microor-ganisms	Terrestrial	Bioaccu-mulation	Biodegradation (%)	
	Algae	Crustaceans	Fish	mg/l		BCF	Aerobic	Anaerobic
Acute	> 100 x S_w (96 h)	0.66	> 100 x S_w	>10,000	N.D.	27	66 (ready)	N.D.
Chronic	N.D.	0.035-0.052 (MATC)*	N.D.	N.D.	N.D.	-	-	-

N.D.: No data found
-: Not relevant for the specific parameter.
*: Maximum acceptable toxicant concentration

Acute toxicity

DEHA is not toxic to algae at or below the water solubility level of DEHA (0.78 mg/l). It should be noted that the test duration in this test was 96 hours, a day longer than standard acute tests for algae (Felder et al., 1986).

A number of acute studies in algae, crustaceans and fish observed toxicity at concentrations above the solubility of DEHA in water (BUA, 1996a; European Commission Joint Research Centre, 2000). However, the acute toxicity for *D. magna* is shown to be 0.66 mg/l in one study performed with low concentrations (Felder et al., 1986), and DEHA is therefore considered very toxic to crustaceans.

Chronic toxicity

The chronic data for crustaceans shows that in a 21d flow through test DEHA had adverse effects on the reproduction of *Daphnia magna.* The maximum acceptable toxicant concentration (MATC) for reproduction (and body length and mortality) ranged from 0.035 to 0.052 mg/l (Felder et al., 1986).

Microorganisms and terrestrial ecotoxicity

DEHA does not seem to have any apparent effects on microorganisms in environmentally relevant concentrations. No data on terrestrial organisms was found.

Bioaccumulation

DEHA has a measured bioaccumulation factor of 27 (Felder et al., 1986) showing that DEHA is not a bioaccumulative substance. There is a discrepancy between the measured and the estimated bioaccumulation, the estimated value being 100 fold higher than the actual measured BCF, which indicate that DEHA is not bioaccumulated as predicted by directly $LogP_{ow}$. This is common for very lipophilic substances.

Aerobic and anaerobic biodegradation

According to the available data there is evidence of ready biodegradability of DEHA (BUA 1996a), but no data are available on inherent or anaerobic biodegradation. A simple mass balance of DEHA on three sewage treatment plants in Denmark (Hoffmann 1996), shows that a 90% reduction is achieved in the plants. However, also that between 15 and 25% of the DEHA plasticiser in the inflow is later found in the sludge, which is comparable to the fate of DEHP.

Environmental assessment

Most of the data on algae, crustacean and fish are reported as '> water solubility'. For the purpose of the environmental assessment these values are evaluated according to Pedersen et al. (1995) and the 50% effect concentration set equal to the water solubility. The lowest observed acute LC_{50} was

identified for *Daphnia magna* for the aquatic environment. For this species a chronic test (reproduction test) result was also found. The endpoint in the reproduction test was MATC, which may be a accepted as a NOEC, and the assessment factor for derivation of PNEC is 100 according to the EU TGD 1996 (three acute and one chronic results). The estimated PNEC is 0.00035 mg/l.

If the chronic test result is not considered as a NOEC, an assessment factor of 1,000 based on the acute test results in a PNEC of 0.00066 mg/l. The most conservative result is obtained using the MATC result, and this is used in assessment presented below. The additional factor of 10 is applied for very lipophilic substances to allow for additional intake *via* food in benthic organisms (EU TGD 1996).

Table 5.2
Environmental Assessment for DEHA

Scenario	Aquatic Surface$_t$	Sediment
Estimation		
Aquatic	0.092	0.4[a]
Worst case		
Aquatic	0.583	2.2[a]

[a] including additional factor 10 due to high lipophilicity ($LogP_{ow} > 5$)

Conclusion

Under worst case assumptions the PEC/PNEC ratio exceeds 1 in the sediment compartment, thus predicting potential effects to organisms living here. In all other cases the aquatic PEC do not exceed the PNEC. A terrestrial risk assessment cannot be performed due to lack of toxicity data.

5.2 O-acetyl tributyl citrate; 77-90-7

5.2.1 Use, emission and exposure

Physical-chemical properties

Citrates are esters of citric acid and these plasticisers are produced with a variety of alcohol groups.

O-acetyl tributyl citrate (ATBC) is a relatively water-soluble plasticiser with measured data ranging from insoluble to 0.005 g/l measured at an unknown temperature. ATBC has an estimated vapour pressure of 4.6×10^{-6} mm Hg. The estimated $LogP_{ow}$ value of 4.3 (HSDB 2000) indicates that this substance is less lipophilic compared to phthalates and many other plasticisers.

Migration

The measured reduced migration potential (household cling to olive oil and acetic acid) of 2.8-4.7 mg/dm^2 indicates that ATBC possesses the potential of migrating from the cling phase to a fatty or aqueous phase in contact with the cling (Plastindustrien i Danmark 1996). The migration is faster, when the receiving phase contains fat. The loss from film to food (cheese) corresponds to 1-6% of the plasticiser in the film (Castle et al., 1988b). ATBC migrates less than diisononyl phthalate (DINP) in a saliva simulant test (Nikiforov, 1999).

Use pattern for compound

The main uses of acetyl tributyl citrate may be in products used in toys, the hospital sector, packaging, printing inks, adhesives, fillers and products containing various amounts of plastic material, cf. Table 4.2.

Exposure in the work place

The EASE calculation focuses on the production and use of printing inks in printed magazines.

The following assumptions are made with regard to the workplace exposure:

- production takes place at a temperature of max. 30 °C
- required legal exhaust ventilation is in place
- contact with the substance will only take place incidentally, e.g. in relation to cleaning and maintenance of production equipment.

Possible main exposure routes in the workplace is:

- inhalation.

Based on this scenario, the EASE calculation gives the results shown in Table 5.1.

Table 5.1
Estimated values of ATBC in the working environment according to the EASE calculation

Route of exposure	EASE value	Unit
Vapour concentration in air for workers	0.5-3	ppm
Vapour concentration in air for workers	8.37-50.2	mg/m^3
Potential dermal uptake for workers	0	mg/kg/day

Consumer exposure

Two scenarios have been selected for evaluation of consumer exposure to ABTC: a limited exposure from plasticiser use in printing inks and an exposure of a vulnerable group – infants chewing on a teething ring.

Printing ink

The selected scenario is the exposure of an adult half an hour a day reading a printed magazine. Based on this scenario, the EASE calculation gives the results shown in Table 5.2.

Table 5.2
Estimated potential daily intake of ATBC by consumers according to the EASE calculation

Route of exposure	Daily intake in mg/kg bw/day	Ratio of the ADI
Inhalatory intake	5.82×10^{-6}	*
Dermal uptake	8.04×10^{-13}	*
Oral intake	0	*
Total chronic uptake via different routes	4.36×10^{-6}	*
Total acute uptake via different routes	0	*

*: The ADI has not been established. An estimated ADI of 1 mg/kg bw/d is calculated in Nikiforov (1999)

Teething ring

A special EASE-scenario has been set up for the use of ATBC in teething rings used by small children. It is assumed that use occurs 3 hours pr day (10 events of 20 minutes each). In the scenario, uptake through the mucous membranes in the gums is not considered as the absorption rate is unknown. The result of the EASE-calculation is shown in Table 5.3.

Table 5.3
Estimated potential daily intake of ATBC by contact with toys by consumers according to the EASE calculation

Route of exposure	Daily intake in mg/kg bw/day	Ratio of the ADI
Inhalatory intake	3.85×10^{-10}	*
Dermal uptake	0.06	*
Oral intake	0	*
Total chronic uptake via different routes	0.06	*
Total acute uptake via different routes	0	*

*: The ADI has not been established. An estimated ADI of 1 mg/kg bw/d is calculated in Nikiforov (1999).

The EASE calculation does not take exposure via mucous membranes into consideration nor swallowing of saliva. An estimated total oral intake from mouthing of plasticised toys must therefore be expected to be higher. However, for ATBC a preliminary risk characterisation has been carried out on behalf of the producer (Nikiforov, 1999) based on American and Dutch risk characterisations for DINP. Considering that migration of ATBC was approx. one third of DINP under identical conditions, an expected daily intake (EDI) after mouthing 11 cm^2 of surrogate toy for four 15 minutes periods amounts to an average of 0.006 mg/kg bw/day and 0.094 mg/kg bw/day for the 95^{th} percentile. These results apply to infants 3-12 months old and assuming all plasticiser in saliva is bioavailable.

In the EASE scenario the exposure time is considerably higher (200 minutes compared to 60 minutes). Adjustment for this yields 0.31 mg/kg bw/day and adding the 0.06 mg/kg bw/day results in a total EDI of 0.37 mg/kg bw/day. An estimated ADI of 1 mg/kg bw/d is calculated in Nikiforov (1999).

Environmental exposure of humans

The amount established in 'Usage' section is used to calculate exposure for a number of environmental compartments by EU TGD/EUSES.

Table 5.4
The estimated human doses of ATBC through intake of water, fish, leaf of crops, roots of crops, meat, milk and air.

ATBC		Estimation (~550 t)	Worst case (10,700 t)
		mg/kg/d	mg/kg/d
Drinking water		2.9×10^{-6}	8.5×10^{-6}
Fish	BCF estimated*	0.00031	0.0009
Plants	Leaf crops	0.000006	0.000106
	Root crops	2×10^{-6}	8×10^{-6}
Meat		7×10^{-8}	9.6×10^{-7}
Milk		4×10^{-8}	5.7×10^{-7}
Air		2×10^{-8}	3.6×10^{-7}
Total regional		0.00031	0.00102

* Measured BCF value not available

Exposure in the environment

The estimated concentration levels of ATBC indicate a high concentration in the particulate phases (sediment and soils).

Table 5.5
The estimated regional concentrations of ATBC in water, soil and air.

Compartment		Aquatic			Terrestrial			Air
ATBC	$Surface_t$	$Surface_d$	Sediment	Natural	Agricul-tural	Porewa-ter of agri. soil.	Industrial	
	mg/l	mg/l	mg/kg	mg/kg	mg/kg	mg/l	mg/kg	mg/m3
Estimation (~550 t)	0.0002	0.0002	0.027	0.00002	0.00018	2.3×10^{-6}	0.00096	1×10^{-7}
Worst case	0.0006	0.0006	0.078	0.00034	0.00060	7.7×10^{-6}	0.0186	1.7×10^{-6}

Secondary poisoning

Only estimated BCF values are available. These lead to relatively high concentrations in fish.

Table 5.6
The estimated regional concentrations of ATBC in fish, plants, meat and milk.

Articles of food	Wet fish		Plants			Meat	Milk
ATBC	Estimate	Measured	Roots	Leaves	Grass		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kgww	mg/kgww	mg/kgww
Estimation (~550 t)	0.19	N/A.	0.0004	0.0004	0.0004	0.00002	4.9×10^{-6}
Worst case (10,700 t)	0.55	N/A.	0.0014	0.0062	0.0062	0.00022	7.08×10^{-5}

N/A.- not available. Data needed to perform estimation of BCF not available.

5.2.2 Health assessment

The most significant toxicity data on ATBC are presented in Table 5.1.

Table 5.1
Selected toxicity data on ATBC

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Acute oral toxicity	Rat	N.D.		LD_{50}=31.4 g/kg bw	1
Acute inhalation toxicity	-				
Acute dermal toxicity	-				
Acute toxicity, other routes	Rabbit	N.D.	0.1 g/kg bw (i.v.)	Increased motor activity and respiration.	3
	Rabbit	N.D.	Unspecified dose (i.v.)	Depressive effect on blood pressure and respiration.	3
	Mouse and rat	N.D.	0.4 g/kg bw (i.p.)	Severe signs of CNS toxicity.	3
Irritation - skin	Rabbit	N.D.	N.D.	Not irritating.	4
- eye	Rabbit	N.D.	5%	Temporarily abolished corneal reflex action	3
	Rat	N.D.	N.D.	Moderate irritation.	4
Sensitisation	Guinea pig	Maximisation test	N.D.	Not sensitising	4
Repeated dose toxicity	Rat, Wistar	Repeated oral dose, OECD 408	100, 300, 1000 mg/kg bw/day 90 days	Haematological and biochemical changes. Increased liver weight at top dose. NOAEL = 100 mg/kg bw/day.	4
Genetic toxicity	*Salmonella typhimurium*	Ames test, +/-	N.D.	Not mutagenic	2
	Rat lymphocytes	+/-	N.D.	No chromosomal aberrations	4
	Rats	Unscheduled DNA synthesis	800, 2000 mg/kg, gavage	No UDS	4
Reproductive / developmental toxicity	Rat, Sprague Dawley	2-generation reproduction, OECD 416	0, 100, 300, 1000 mg/kg/day	Decreased bodyweights NOAEL = 100 mg/kg bw/day	4
Carcinogenicity	Rat, Sherman	N.D. Old guideline. Feeding study	0, 200, 2000, 20000 ppm. 2 years	No significant exposure related findings. Results cannot be evaluated (old guideline).	4
Experience with human exposure	Human	Sensitisation test	N.D.	No sensitisation or irritation.	4

References: 1) HSDB (2000), 2) CCRIS (2000), 3) TNO BIBRA International Ltd (1989), 4) CSTEE (1999)

Observations in humans	There was no evidence of irritation or sensitisation in a sensitisation test in humans. No further information is available.
Acute toxicity	Acetyl tributyl citrate has exhibited low acute oral toxicity in laboratory animals (LD_{50}=31.4 g/kg) (HSDB, 2000). Studies where a single dose (0.1 - 0.4 g/kg bw) of ATCB has been administered by the intraperitoneal or intravenous route have indicated that the central nervous system and blood are the critical organs in various species (rodents) of laboratory animals (TNO BIBRA, 1989).
Irritation	Available data indicate no irritation of skin and moderate eye irritation (CSTEE, 1999; TNO BIBRA, 1989).
Sensitisation	O-acetyl tributyl citrate was not sensitising in a guinea pig maximisation test (CSTEE, 1999).
Repeated dose toxicity	A NOAEL of 100 mg/kg bw/day was established in a 90 gavage study in rats where haematological and biochemical changes and increased liver weights were observed at higher doses (CSTEE, 1999).
Genetic toxicity	Acetyl tributyl citrate has not been shown to be mutagenic in the reported Ames bacterial assay. ATCB did not cause chromosomal aberrations in rat lymphocytes or unscheduled DNA synthesis in rats treated by gavage at 800 or 2,000 mg/kg bw. The negative UDS study indicated that the *in vivo* genotoxic potential of ATCB is low or absent (CSTEE 1999).
Long term toxicity	In a two-year carcinogenicity study, rats were fed doses of 200; 2,000 and 20,000 ppm ATBC in the diet. No significant dose related toxicological findings were reported. The study is however not according to modern guidelines and the carcinogenicity of ATBC cannot be evaluated properly based on these findings (CSTEE, 1999). In a two-generation reproduction study in rats according to OECD guideline 416, rats were fed doses of 100, 300 and 1,000 mg/kg bw/day. Decreased body weights in F1 males from 300 mg/kg bw/day and F0 males at 1000 mg/kg bw/day were observed. A NOAEL of 100 mg/kg bw/day was established (CSTEE, 1999).
NOAEL/LOAEL	Lowest reported NOAEL is 100 mg/kg bw/day (repeated dose 90 days oral toxicity in rats and reproductive toxicity rats) (CSTEE, 1999).
Summation/Conclusion on health	Sufficient data were not found to make a profound health assessment. ATCB has very low acute toxicity. LD_{50} in rats was reported to be 31.4 g/kg bw. O-acetyl tributyl citrate was not found to be an irritant to skin or sensitising. Moderate eye irritation has been observed. (CSTEE, 1999; TNO BIBRA, 1989). In the reviewed literature o-acetyl tributyl citrate has not been found mutagenic. ATCB did not cause chromosomal aberrations in rat lymphocytes or unscheduled DNA synthesis in rats treated by gavage. The negative UDS study indicated that the in vivo genotoxic potential of ATCB is low or absent (CCRIS, 2000; CSTEE, 1999)

Repeated dose toxicity in rats included haematological and biochemical changes and increased liver weights. A NOAEL of 100 mg/kg bw/day was established (CSTEE, 1999).

The carcinogenic potential cannot be evaluated based on the available literature.

Decreased body weights were observed in F1 male rats (300 mg/kg bw/day) and F0 male rats (1,000 mg/kg bw/day) in a 2-generation study. A NOAEL of 100 mg/kg bw/day was established.

Critical effect

Based on the available limited data, the identified critical effect in rats appears to be reproductive toxicity resulting in decreased body weights and repeated dose toxicity resulting in haematological and biochemical changes and increased liver weights.

Classification

Sufficient data are not available to evaluate the classification of the substance for all effects.

Exposure versus toxicity

A comparison between the calculated exposure of consumers and the very limited available toxicological information about ATBC indicates that the selected exposure scenario represents a minor risk to human health.

General exposure of the population may occur through dermal contact with consumer products containing O-acetyl tributyl citrate and ingestion of contaminated food. O-acetyl tributyl citrate has been found in the aquatic environment.

The selected scenario for EASE-calculation of the consumer exposure of o-acetyl tributyl citrate results in low exposures. It is therefore estimated that only a limited contribution of the overall exposure of humans comes from products.

No ADI has been established for ATBC. A preliminary ADI has been estimated to 1 mg/kg bw/day (Nikiforov 1999). An ADI of 0.05 mg/kg bw/day may be assigned on a conservative basis from DEHP proliferation peroxisome data, but it should be mentioned that there is no information in the available literature indicating that ATBC causes peroxisome proliferation.

The selected EASE-scenario for teething rings modelling the exposure of o-acetyl tributyl citrate in children from dermal contact is 6% of a preliminary ADI and similar to the assigned ADI. It should, however, be mentioned that the EASE scenario of exposure to ATCB from toys does not adequately model the oral exposure from plasticisers in teething rings since swallowing of saliva and uptake via the mucous membranes is not included. A different approach including these sources yields seven times the assigned ADI and 37% of the preliminary ADI for infants.

By the oral route, ATBC exhibits low acute toxicity in laboratory animals, but no data have been found describing toxicity by inhalation or dermal toxicity.

With regard to exposure in the working environment, relevant data have not been identified. Exposure may occur through inhalation of dust particles and dermal contact when working in places where O-acetyl tributyl citrate is handled.

The EASE-calculation indicates that the concentration of o-acetyl tributyl citrate in the working environment of the selected scenario can be in quantities of up to 50 mg/m^3. Due to the lack of toxicity data, it is not possible to assess whether this value gives rise to concern.

5.2.3 Environmental assessment

Very few ecotoxicity data was found for ATBC. Biodegradation data has been identified.

Table 5.1
Ecotoxicity and fate data on ATBC.

ATBC	Aquatic (mg/l)				Terrestrial	Bioaccumulation	Biodegradation	
	Algae	Crustaceans	Fish	Microorganisms			Aerobic	Anaerobic
						BCF	28 days	
Acute	N.D.	N.D.	38-60	N.D.	N.D.	1,100 (estimated)	80% at 30 mg/l (inherent)	N.D.
Chronic	N.D.	N.D.	N.D.	N.D.	N.D.	-	-	-

Aquatic and terrestrial ecotoxicity

The only ecotoxicological data identified for ATCB originates in volunteered proprietary information. Two species of typical freshwater test species showed LC_{50}'s ranging from 38-60 and 59 mg/l, respectively (Ecosystems Laboratory 1974). No chronic ecotoxicological data was found.

Bioaccumulation

The estimated BCF indicate that ATBC can be bioaccumulated (Syracuse Research Corporation, 2000). An estimated $LogP_{ow}$ value on 4.3 supports this assumption.

Aerobic and anaerobic biodegradation

Aerobic biodegradation in non-standard test showed a rather slow degradation 26% after 21 days (Ecosystems Laboratory 1974). No data on anaerobic biodegradation was found.

ATBC was degraded 80% in an inherent biodegradation test. The compound is therefore assessed as inherently biodegradable.

Risk assessment

The data available is insufficient for calculating a PNEC according to the EU TGD. If however, a PNEC is based on the single study available a PNEC of approx. 0.04 mg/l is estimated for the aqueous phase, the predicted concentrations (PECs) for surface water and for sediment are 50-500 times lower than PNEC.

Table 5.2
Risk Assessment on ATBC (based on incomplete data set).

Risk assessment	Aquatic Surface$_t$	Sediment
Best guess		
Aquatic	0.005	0.002
Worst case		
Aquatic	0.015	0.005

Based on the relatively slow degradation and lipophilicity of ATBC it is assumed that effects in the environment may be associated with the potential for bioaccumulation in fauna in the receiving environment.

5.3 Di(2-ethylhexyl) phosphate; 298-07-7

Physical-chemical

The water solubility of di(2-ethylhexyl) phosphate (DEHPA) has been measured to 100 mg/l at an unknown temperature. Under the assumption that the solubility was measured at standard temperature, DEHPA is a relatively soluble compound when compared to the other substances investigated.

This substance is an acid with a pK_a in the range of 1.72-2.17, which indicates that this compound is fully dissociated at neutral pH.

DEHPA has an estimated vapour pressure of 4.65×10^{-8} mm Hg. Under the assumption that the estimated vapour pressure is valid at standard temperature, the magnitude of the vapour pressure places DEHPA among the substances investigated that possess a very low vapour pressure.

The measured $LogP_{ow}$ value of 2.67 indicates that this substance is moderately lipophilic agrees with low BCF values (BUA 1996b). The estimated $LogP_{ow}$ value of 6.07 presumably overestimates lipophilicity due to the presence of the dissociable phosphate group. Under the assumption that the measured P_{ow} is valid in natural pH range, DEHPA possess low lipophilicity when compared to the other substances investigated. This substance is also an acid with a pK_a in the range of 1.72-2.12, which indicates that this compound is almost completely dissociated at pH 5-9 (BUA, 1996b).

Migration

No information on the migration potential of DEHPA has been located. Migration of diphenyl 2-ethylhexyl phosphate from food films ranged from 0.1-0.5 mg/dm^2 when measured in a range of fat containing food products (Castle et al, 1988b).

5.3.1 Use, emission and exposure

The group of phosphate plasticisers are triesters of phosphoric acid and includes triaryl and trialkylesters. This group of plasticisers is more resistant to ignition and burning than all the other groups of ester plasticisers and is most often used as flame-retardants in products with specific fire resistant demands.

Use pattern for compound

The main uses of DEHPA may be in PVC-products used in e.g. the hospital sector, packing, cables, profiles and floor and wall coverings, cf Table 4.2.

Exposure in the work place

The EASE-calculation focuses on the production of cables.

The following assumptions are made with regard to the workplace exposure:

- production takes place at a temperature of 180 °C
- required legal exhaust ventilation is in place
- contact with the substance will only take place incidentally, e.g. in relation to cleaning and maintenance of production equipment.

Possible main exposure routes in the workplace:

- inhalation.

Based on this scenario, the EASE calculation provides the results shown in Table 5.1.

Table 5.1
Estimated values of DEHPA in the working environment according to the EASE calculation.

Route of exposure	EASE value	Unit
Vapour concentration in air for workers	0-0.1	ppm
Vapour concentration in air for workers	0-1.34	mg/m^3
Potential dermal uptake for workers	0	mg/kg/day

Consumer exposure

The EASE-calculation focuses on use of cables in a normal private house.

Possible main routes of consumer exposure:

- inhalation
- dermal contact with consumer goods
- ingestion of contaminated food.

Based on this scenario, the EASE calculation gives the results shown in Table 5.2.

Table 5.2
The estimated potential daily intake of DEHPA by consumer according to the EASE calculation

Route of exposure	Daily intake in mg/kg bw/day	Ratio of the ADI
Inhalatory intake	5.82×10^{-6}	*
Dermal uptake	8.04×10^{-13}	*
Oral intake	0	*
Total chronic uptake via different routes	4.36×10^{-6}	*
Total acute uptake via different routes	0	*

*: The ADI has not been established. Other phosphorous acid dialkyl esters have been allocated a group restriction value of 0.05 mg/kg bw/d based on DEHP peroxisome proliferation data (SCF, 2000).

Environmental exposure of humans

The EUSES-calculation indicates that humans may by exposed for the substance as illustrated in Table 5.3.

Table 5.3
The estimated human doses of DEHPA through intake of water, fish, leaf of crops, roots of crops, meat, milk and air.

DEHPA		Estimation (~2,000 t)	Worst case (10,700 t)
		mg/kg/d	mg/kg/d
Drinking water		1.1×10^{-5}	5.7×10^{-5}
Fish	BCF measured	3.7×10^{-6}	2.0×10^{-5}
Plants	Leaf crops	1.3×10^{-5}	6.9×10^{-5}
	Root crops	2.1×10^{-6}	1.1×10^{-5}
Meat		3.7×10^{-9}	1.9×10^{-8}
Milk		4.6×10^{-9}	2.4×10^{-8}
Air		4.4×10^{-9}	2.3×10^{-8}
Total regional		0.00003	0.00016

Exposure in the environment

The estimated concentration levels of DEHPA show that concentrations in the aqueous compartment are relatively high compared to other plasticisers due to the high solubility of DEHPA.

Table 5.4
The estimated regional concentrations of DEHPA in water, soil and air.

Compartment	Aquatic			Terres-trial				Air
DEHPA	$Surface_t$	$Surface_d$	Sediment	Natural	Agricul-tural	Porewa-ter of agri. soil.	Industrial	
	mg/l	mg/l	mg/kg	mg/kg	mg/kg	mg/l	mg/kg	mg/m3
Estimation (~2,000 t)	0.0004	0.0004	0.0017	0.0005	0.0003	6.6×10^{-5}	0.0049	2.1×10^{-8}
Worst case (10,700 t)	0.0020	0.0020	0.0090	0.0026	0.0013	3.5×10^{-4}	0.0256	1.1×10^{-7}

Secondary poisoning

DEHPA is not expected to bioaccumulate and there is no anticipation of secondary poisoning.

Table 5.5
The estimated regional concentrations of DEHPA in fish, plants, meat and milk.

Articles of food	Wet fish		Plants			Meat	Milk
DEHPA	estimate	measured	Roots	Leaves	Grass		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kgww	mg/kgww	mg/kgww
Estimation (~2,000 t)	0.014	0.002	0.0004	0.0008	0.0008	9×10^{-7}	6×10^{-7}
Worst case (10,700 t)	0.073	0.011	0.0020	0.0040	0.0040	4.8×10^{-6}	3.0×10^{-6}

5.3.2 Health assessment

The most significant toxicity data on DEHPA are presented in Table 5.1.

Table 5.1
Selected toxicity data on DEHPA.

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Acute oral toxicity	Rat	N.D.		LD_{50}=4,742 mg/kg bw	2
Acute inhalation toxicity	Dogs	N.D.	380 ppm, 8 hours	Death occurred (no further info)	2
Acute dermal toxicity	Rabbit	N.D.	1.25 ml/kg, 24 hours	LD_{50}=1,200 mg/kg bw	2
Acute toxicity, other routes	Rat	N.D.	i.p.	LD_{50}=50-100 mg/kg bw	2
Irritation - skin	Rabbit	Occlusive test, intact skin	10 µl (24 hours)	Necrosis after 24 hours	2
- eye	Rabbit	N.D.	5 µl (1%)	Corrosive to cornea	2
Sensitisation	-				
Repeated dose toxicity	Rat (Sprague Dawley)	Oral	25, 100, 200 mg/kg bw (5 days)	Significant increase in relative liver weights at 100 and 200 mg/kg bw/day. Potent induction of P450b+e system.	2
Genetic toxicity	*Salmonella typhimurium*	Ames test, +/-	4-2,500 µg/plate (cytotoxic from 100 g/plate)	Not mutagenic	2
Reproductive / developmental toxicity	-				
Carcinogencity	-				
Experience with human exposure	Human	Irritation test	N.D.	Smarting of skin and 1st degree burn	1
	Human	Inhalation	2 ppm	Weakness, irritability and headache	1

References: 1) HSDB (2000), 2) BUA (1996b)

Observations in humans Inhalation of 2 ppm showed weakness, irritability and headache.

DEHPA caused irritation of eyes and first and second degree skin burns.

Acute toxicity An oral LD_{50} in rats of 4,742 mg/kg is reported representing low acute toxicity. The observed dermal LD50 leads to classification with R21 *(Harmful in contact with skin).*

Irritation/corrosion The substance is reported to corrosive to skin and eyes in rabbits.

Sensitisation No information is available on skin sensitisation.

A repeated dose toxicity study in rats dosed for five days showed a significant increase in relative liver weights at 100 and 200 mg/kg bw and induction of the P450b+e system.

Genetic toxicity

DEHPA has not been shown to be mutagenic (BUA 1996b).

Long term toxicity

Concerning reproductive and teratogenic effects of DEHPA, relevant data have not been identified.

NOAEL/LOAEL

Relevant data have not been identified in the investigation.

Summation/Conclusion on health

Sufficient data were not found to make a profound health assessment. However, inhalation of 2 ppm caused weakness, irritability and headache in humans.

Acute oral toxicity of di(2-ethylhexyl) phosphate to rats seems to be low, whereas dermal toxicity to rabbits is pronounced.

Di(2-ethylhexyl) phosphate exhibits strong corrosive effect in cornea at 5 µl doses (1% solution) as well as corrosive effects on rabbit skin. Mutagenic activity has not been observed.

Data establishing reproductive toxicity or teratogenicity were not found.

Critical effect

All endpoints have not been sufficiently investigated. Dermal toxicity and local corrosive effects on skin and eyes observed in rabbits seem to be the most severe effects.

Classification

Sufficient data are not available for classification. DEHPA has been classified by Bayer AG in 1993 as C (*Corrosive*); R34 (*Causes burns*) and Xn (*Harmful*); R21 (*Harmful in contact with skin).*

Exposure versus toxicity

A comparison between the calculated exposure of consumers and the available toxicological information about DEHPA indicates that the selected exposure scenario represents a minor risk to human health. This is based on calculated exposure values several orders of magnitude lower than the observed effect levels in animal studies.

General exposure of the population may occur through dermal contact with consumer products containing di(2-ethylhexyl) phosphate and ingestion of contaminated food.

Based on the selected scenario, the EASE-calculation indicates that the exposure of di(2-ethylhexyl) phosphate in consumers represents very small values and constitutes a limited contribution to the overall exposure of consumers.

The values are at the same level or below the values arising from the indirect exposure by contaminated food.

Concerning exposure in the working environment, inhalation of 2 ppm has been observed to cause weakness, irritability and headache. Exposure may occur through inhalation of dust particles and dermal contact when working in places where di(2-ethylhexyl) phosphate is handled.

The EASE-calculation indicates that the concentration of di(2-ethylhexyl) phosphate in the working environment related to the selected scenario can

be in quantities up to 0.1 ppm. This value is only a factor 20 from the concentration that may cause adverse effects from inhalation.

5.3.3 Environmental assessment

Aquatic and terrestrial ecotoxicity

The ecotoxicological data from acute standard tests indicate, that di(2-ethylhexyl) phosphate is harmful to algae (BUA 1996b), crustaceans (US EPA 2000) and fish (BUA 1996b), i.e. the L(E)C_{50}'s are in the 10-100 mg/l range. Slightly increased acute toxicity is, not surprisingly, seen in the tests of longer duration. Data from true chronic tests are not available, but growth inhibition is reported down to 0.3 mg/l in fish and microorganisms (HSDB 2000). The nature of the tests has not been identified.

The respiration of the micro-organism *Thiobacillus ferrooxidans* was inhibited 68% in a three hours test (BUA 1996b). No data on terrestrial ecotoxicity was identified.

Table 5.1
Ecotoxicity and fate data on DEHPA.

DEHPA	Aquatic (mg/l)				Terrestrial	Bioaccumulation	Biodegradation	
	Algae	Crustaceans	Fish	Microorganisms			Aerobic	Anaerobic
						BCF	28 days	
Acute	50-100	42-84	20-56	443 (IC_{68}, 3h)	N.D.	1.1-6	0-17%, 75%	N.D.
Chronic	N.D.	N.D.	0.3-100 Growth inhibition	0.3-100 Growth inhibition	N.D.	-	-	-

Bioaccumulation

The bioaccumulation of DEHPA is low. A BCF of only up to 6 has been measured in fish (BUA 1996b). The bioaccumulation potential expressed by $LogP_{ow}$ is also less than three (2.67), and significant bioaccumulation is not expected.

Aerobic and anaerobic biodegradation

Inconsistent data on the biodegradability of di(2-ethylhexyl) phosphate are quoted in BUA (1996b). At lower substrate concentration (30 mg/l) the substance does not biodegrade, but a three times higher concentration the substance is readily biodegradable. The compound is assessed as inherently biodegradable

No data on anaerobic degradation is available. There is no data for DEHPA from sludge, but three phosphate triesters has been found in 11 of 20 sewage sludge samples at an average of 0.2 to 1.8 mg/kg dryweight (Kristensen et al., 1996).

Risk assessment

The PNEC is calculated with a safety factor of 1000 since no chronic data is available. The lowest standard test value is a fish test value of 20 mg/l, corresponding to a PNEC of 0.02 mg/l.

Table 5.2
Risk Assessment on DEHPA.

Risk assessment	Aquatic	
	$Surface_t$	Sediment
Estimation		
Aquatic	0.019	0.01
Worst case		
Aquatic	0.1	0.05

Conclusion

The PEC/PNEC ratio does not exceed 1 in any aquatic compartment and hereby predict no potential effect on organisms in the aquatic water and sediment compartments.

A terrestrial risk assessment cannot be performed due to lack of toxicity data.

5.4 Tri(2-ethylhexyl) phosphate; 78-42-2

5.4.1 Use, emission and exposure

Physical-chemical properties

Tri(2-ethylhexyl) phosphate (TEHPA) is in general produced and used similarly to DEHPA.

The solubility data on TEHPA ranges from insoluble in water to <0.5 - <100 mg/l at 18-24 ^oC with one exact solubility of 0.6 mg/l at 24 ^oC. The exact water solubility on TEHPA indicates that this substance possess a low water solubility.

TEHPA has an estimated vapour pressure of 8.3×10^{-7} mm Hg at 25 ^oC. The magnitude of the vapour ranges in the lower end of the 11 substances investigated.

The available $LogP_{ow}$ values on TEHPA ranges from 0.8-5.0. Indications of the origin and pH at measurement of the high-end values are however not available (BUA 1996b). The measured BCF value on TEHPA of 2.4-22 does suggest the $LogP_{ow}$ values in the high end of the $LogP_{ow}$ range are overestimates. Similarly to DEHPA, this substance may also be dissociated at neutral pH. TEHPA is therefore among the substances investigated that possesses a low lipophilicity. However, as a worst case assumption a $LogP_{ow}$ of 5 has been used in calculating TEHPA in the sediment compartment.

Migration

No data has been located on the migration potential of TEHPA.

Exposure in the work place

The EASE-calculation focuses on the production of cables.

The following assumptions are made with regard to the workplace exposure:

- production takes place at a temperature of 180 °C
- required legal exhaust ventilation is in place
- contact with the substance will only take place incidentally, e.g. in relation to cleaning and maintenance of production equipment.

Possible main exposure routes in the workplace:

- inhalation of vapours.

Based on this scenario the EASE calculation gives the results shown in Table 5.1.

Table 5.1
Theoretical values of TEHPA in the working environment according to the EASE calculation

Route of exposure	EASE value	Unit
Vapour concentration in air for workers	0.5-3	ppm
Vapour concentration in air for workers	9.04-54.2	mg/m^3
Potential dermal uptake for workers	0	mg/kg/day

Consumer exposure

In the EASE calculation focus is on use of cables in a private household.

Possible main routes of consumer exposure:

- inhalation
- dermal contact with consumer goods
- ingestion (children).

Based on this scenario, the EASE calculation gives the results shown in Table 5.2.

Table 5.2
The theoretical potential daily intake of TEHPA by consumers according to the EASE calculation

Route of exposure	Daily intake in mg/kg bw/day	Ratio of the ADI
Inhalatory intake	5.82×10^{-6}	*
Dermal uptake	8.04×10^{-13}	*
Oral intake	0.0286	*
Total chronic uptake via different routes	0.0286	*
Total acute uptake via different routes	0	*

*: The ADI has not been established. Other phosphorous acid dialkyl esters have been allocated a group restriction value of 0.05 mg/kg bw/d based on DEHP peroxisome proliferation data (SCF, 2000).

Environmental exposure of humans

The amount established in 'Usage' section is used to calculate exposure for a number of environmental compartments by EU TGD/EUSES. The dose is mainly derived from consumption of root crops and meat. This is due to the $LogP_{ow}$ of TEHPA leading to a slight accumulation in agricultural soil. No measured data are available for accumulation in plants.

Table 5.3
The estimated human doses of TEHPA through intake of water, fish, leaf of crops, roots of crops, meat, milk and air.

TEHPA		Estimation (~2,200 t)	Worst case (10,700 t)
		mg/kg/d	mg/kg/d
Drinking water		0.00001	0.00535
Fish	BCF measured	0.00002	0.00008
Plants	Leaf crops	0.00002	0.00008
	Root crops	0.0007	0.0032
Meat		0.00046	0.000002
Milk		3×10^{-7}	1×10^{-6}
Air		8×10^{-8}	4×10^{-7}
Total regional		0.0012	0.0087

Exposure in the environment

The estimated concentration levels of TEPHA reflect the relatively high aqueous concentration due to the high solubility with a limited estimated association with particles (sediment and soils).

Table 5.4
The estimated regional concentrations of TEHPA in water, soil and air.

Compartment	Aquatic			Terres-trial				Air
TEHPA	$Surface_t$	$Surface_d$	Sediment	Natural	Agricul-tural	Porewa-ter of agri. soil.	Industrial	
	mg/l	mg/l	mg/kg	mg/kg	mg/kg	mg/l	mg/kg	mg/m^3
Estimation (~2,200 t)	0.0005	0.0005	0.10	0.008	0.05	0.0004	0.2	4×10^{-7}
Worst case (10,700 t)	0.0022	0.0022	0.50	0.037	0.24	0.0019	1.2	1.7×10^{-3}

Secondary poisoning

TEHPA may dissociate in the aqueous environment and the measured and estimated accumulation potential may therefore not imply risk of secondary poisoning in the environment.

Table 5.5
The estimated regional concentrations of TEHPA in fish, plants, meat and milk.

Articles of food	Wet fish		Plants			Meat	Milk
TEHPA	estimate	measured	Roots	Leaves	Grass		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kgww	mg/kgww	mg/kgww
Estimation (~2,200 t)	0.7	0.01	0.1	0.001	0.001	0.0001	0.00003
Worst case (10,700 t)	3.4	0.05	0.6	0.005	0.005	0.0005	0.00016

5.4.2 Health assessment

The most significant toxicity data on TEHPA are presented in Table 5.1.

Table 5.1
Selected toxicity data on TEHPA.

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Acute oral toxicity	Mouse	N.D.		LD_{50}>12,800 mg/kg bw	1
	Rat	N.D.		LD_{50}>2000 mg/kg bw	4
	Rat	N.D.		LD_{50}=37,080 mg/kg bw	4
	Rat	N.D.		LD_{50}=39,800 mg/kg bw	4
	Rabbit	N.D.		LD_{50}=46,000 mg/kg bw	4
Acute inhalation toxicity	Rat	N.D.	450 mg/m^3, duration unknown.	No mortality	4
	Guinea pig	N.D.	450 mg/m^3, 0.5 hours	LC_{50}=450 mg/m^3/30 min	3, 4
Acute dermal toxicity	Rabbit	N.D.	N.D.	LD_{50}=18,400 mg/kg bw	4
Acute toxicity, other routes	-				
Irritation - skin	Rabbit	Applied to shaved skin.	(24 hours)	Moderate erythema within 24 hours.	4
	Rabbit		10-20 ml	Mortality after single application.	4
- eye	Rabbit	N.D.	0.1-0.5 ml (24 hours).	Moderate conjunctivitis which cleared up after 24 hour.	4
	Rabbit	N.D.	0.01-0.05 ml	Light irritation.	4
Sensitisation	Guinea pig			Not sensitising	4
Repeated dose toxicity	Mouse (B6C3F1)	Oral	0, 500, 1000, 2000, 4000, 8000 mg/kg bw (13 weeks, 5 days /week).	Dose dependent gastritis, lowest dose 500 mg/kg bw. Decrease in bw gain. NOEL<500 mg/kg bw.	4
	Rat (Crj:CD(SD))	Oral	30, 100, 1000 mg/kg bw, (28 days).	Reduced protrombin time (♀) and increased partial tromboplastin time (♂). Reduced serumcholineesterase activity. NOEL= 100 mg/kg bw	4
	Rat (Sherman)	Oral	110-1550 mg/kg bw/day (30 days)	Reduced bodyweight gain. NOEL=430 mg/kg bw/day	4
	Monkey (Rhesus)	Inhalation, average particle size=4.4 μm.	10.8, 26.4, 85 mg/m3 (12 weeks, 5 days/weeks, 6 hours/day).	No effects	4
	Dog	Inhalation, aver-	10.8, 26.4, 85		4

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
		age particle size=4.4 μm.	mg/m3 (12 weeks, 5 days/weeks, 6 hours/day).		
	Rabbit (New Zealand)	Dermal	92 mg/animal/day (5 days/week, 3-17 days) 10-20 appl.	Hyperkeratose, mild parakeratose, acute dermatitis, thickening of epidermis. Effects disappeared.	4
Genetic toxicity	*Salmonella typhimurium*	Ames test, +/-	N.D.	Not mutagenic.	4
	CHO cells	In vitro mammalian cell gene mutation test, +/-	Up to 1670 μg/ml.	No chromosome aberration.	4
	Rat	Micronucleus test	0, 0.25, 0.50 mg/l air (2 weeks, 5 days / week, 6hrs/day	No micronuclei	4
Reproductive / developmental toxicity	-				
Carcinogenicity	Mouse (B6C3F1)	N.D. (gavage)	0, 500, 1000 mg/kg 5 days/week (102-104 weeks)	Increased incidence of hepatocellular carcinoma in female mice at 1000 mg/kg bw. No evidence of carcinogenicity in male mice..	1, 2
	Rat /Fisher 344)	N.D. (gavage)	♀: 1000 or 2000 mg/kg bw ♂: 2000 or 4000 mg/kg bw	♀: No evidence of carcinogenicity ♂: Equivocal evidence of carcinogenicity (increased incidence of pheochromocytomas in adrenal glands.	1
Experience with human exposure	Human	Irritation test, underarm	24 hours	No irritation	4

References: 1) HSDB (2000) 2) CCRIS (2000) 3) NTP (2000) 4) BUA (1996b)

Observations in humans A 24 hours exposure of the underarm on six test persons did not result in any irritation of the skin.

Acute toxicity Tri(2-ethylhexyl) phosphate appears to have very low acute oral toxicity. LD_{50} in rats was more than 37.08 g/kg and LD_{50} was approx. 46.0 g/kg in rabbits.

Irritation Tri(2-ethylhexyl) phosphate may produce moderate erythema in skin irritation test and slight irritation to eyes.

Sensitisation Sufficient data on skin sensitisation was not found.

Repeated dose toxicity Repeated dose toxicity observed in rats involved haematological changes and reduced body weight gain.

Slight behavioural changes and minor chronic infection in lungs were observed in dogs administered 10.8, 26.4, 85 mg/m^3 (12 weeks, 5 days/week, 6 hrs/day). No effects were observed in monkeys receiving the same treatment.

Genetic toxicity

Based on the available data, TEHPA cannot be regarded as mutagenic and has not been found genotoxic in chromosome aberration test and micronuclei assays. Neither tri-n-ethyl phosphate nor tri-n-octyl phosphate were found mutagenic in *Salmonella* test (Zieger et al., 1987).

Long term toxicity

A slight evidence of carcinogenicity was observed in female mice and equivocal evidence in male rats (HSDB 2000). Based on the evaluation as slightly carcinogenic in mice and not mutagenic and genotoxic, it has been concluded by an ECETOC working group that TEPHA is unlikely to be carcinogenic to humans (BUA 1996b).

Data on reprotoxicity, embryotoxicity and teratogenicity were not found.

NOAEL/LOAEL

In repeated dose toxicity tests, the lowest NOEL of 100 mg/kg for TEHPA was observed in male rats was following 28 days exposure.

Critical effect

Based on the available data the critical effect appears to be heamatological changes from repeated dose toxicity after oral administration in rats and local effects on skin and eyes.

Classification

TEHPA has been classified according to the substance directive by Bayer AG in 1993 as follows: Xi (*Irritant);* R36/38 *(Irritating to skin and eyes).*

Summary of known toxicity

Tri(2-ethylhexyl) phosphate appears to have slight acute oral toxicity.

Slight neurotoxic effects were observed in dogs administered 10.8, 26.4, 85 mg/m^3 (12 weeks, 5 days/week, 6 hrs/day). Based on tests in animals, tri(2-ethylhexyl) phosphate may produce moderate irritation of skin and eyes, but a 24 hours exposure of the underarm on six test persons did not result in any irritation of the skin although moderate erythema is observed in exposed rabbits. Repeated dose toxicity studies in rats have shown haematological changes at concentrations above the NOEL of 10 mg/kg bw. Available studies indicate that there slight evidence of carcinogenicity in female mice and equivocal evidence in male rats. An ECETOC working group ha concluded that TEHPA is unlikely to be carcinogenic in humans.

Exposure versus toxicity

A comparison between the calculated exposure of consumers and the available toxicological information about TEHPA indicates that the selected exposure scenario represents a minor risk to human health, although moderate erythema is observed in exposed rabbits.

General exposure of the population may occur through dermal contact with consumer products containing tri(2-ethylhexyl) phosphate and ingestion of contaminated food. Based on the selected scenario, the EASE-calculation indicates that the consumer exposure to tri(2-ethylhexyl) phosphate is relatively small and constitutes a limited contribution to the overall exposure of humans. Concerning exposure in the working environment exposure may occur through inhalation of dust particles and dermal contact when working in places where tri(2-ethylhexyl) phosphate is handled.

The EASE-calculation indicates that the concentration of tri(2-ethylhexyl) phosphate in the working environment of the selected scenario can reach

levels of up to 55 mg/m^3 and 3 ppm. Inhalation of concentrations of this magnitude has produced high mortality in rats.

5.4.3 Environmental assessment

Generally, data on environmental effects from TEHP from the acute aquatic test systems are available. In the following the most sensitive data are presented.

Table 5.1
Ecotoxicity and fate data on TEHPA.

TEHPA	Aquatic (mg/l)				Terrestrial	Bioaccumulation	Biodegradation (%)	
	Algae	Crustaceans	Fish	Microorganisms			Aerobic	Anaerobic
						BCF	28 days	
Acute	50-100 (48 hrs)	>1.0	100 (LC_0)	>100 (3 hrs)	N.D.	2-22	0	25 (1.4 mg/l, 70 days)
Chronic	N.D.	N.D.	N.D.	N.D.	N.D.	-	-	-

Aquatic and terrestrial ecotoxicity

Based on the available data TEHPA is not toxic to aquatic organisms at TEHPA water solubility level (up to 0.7 mg/l).

The available acute data on ecotoxicity show that TEHPA is harmful to algae, but the test duration is only 48 hours and not 72 hours as prescribed in the recommended method. The toxicity is only described as a range. A test on the ciliate *Tetrahymena pyriformis* is also available, here the $LC_{50}$was 10 mg/l (Yoshioka et al., 1985).

No acute effects were seen on crustaceans in a low range study (Bayer 1999) or up to the solubility limit of 1.0 mg/l (BUA 1996b).

TEHPA is not toxic to fish. In an acute 96 hours fish test with *Brachydanio rerio* LC_0 was more than 100 mg TEHPA/l (Bayer 1999).

No chronic data was available.

Bioaccumulation

The available measured BCF values indicate that TEHPA is not bioaccumulative Chemicals Inspection and Testing Institute, 1992). Log P_{ow} values range from 0.8 to 5.04 predicting that TEHPA range from not bioaccumulative to bioaccumulative.

Aerobic and anaerobic biodegradation

TEHPA is not readily biodegradable according to the available aerobic ready biodegradation data (Chemicals Inspection and Testing Institute, 1992). The compound is slowly biodegraded under anaerobic conditions when present in weak solutions.

There is no data for TEHPA itself in Denmark, but three other phosphate triesters were found in 11 of 20 sewage sludge samples at an average of 0.2 to 1.8 mg/kg dryweight (Kristensen et al., 1996) suggesting incomplete degradation in sewage treatment plants.

Risk assessment

The PNEC is calculated with a safety factor of 1000 since data is available for algae, crustacean and fish, and no chronic data is available (Pedersen et al., 1995).

The lowest aquatic EC/LC_{50} is 50, corresponding to an aquatic PNEC of 0.05 mg/l. In the following Table 5.2 the result of the risk assessment is presented.

Table 5.2
Risk Assessment on TEHPA

Risk assessment	Aquatic	
	$Surface_t$	Sediment
Best guess		
Aquatic	0.01	0.001
Worst case		
Aquatic	0.05	0.005

According to the risk assessment the PEC will not exceed the PNEC in the aquatic compartment.

No ecotoxocity data were available on organisms living in the neither in the sediment or in soil.

5.5 Tri-2-ethylhexyl trimellitate; 3319-31-1

The family of trimellitates, pyromellitates and other polycarboxylic acid esters are used for heat resistant plasticised PVC articles due to their exceptional thermal properties. Trimellitates are similar to phthalates in compatibility and plasticising effect.

5.5.1 Use, emission and exposure

Physical-chemical properties

This group is esters of trimellitic acid (1,2,4-benzene tricarboxylic acid) and generally have a higher molecular weight and corresponding lower vapour pressure resulting in a lower migration potential to aqueous solutions compared to phthalates and other plasticisers.

The available solubility data of Tri-2-ethylhexyl trimellitate (TETM) ranges from <100-100 mg/l at 20-25 ^{o}C. The upper end of the water solubility range places TETM among the relatively soluble substances investigated.
TETM has an estimated vapour pressure of 3.94×10^{-11} mm Hg at 25 ^{o}C, which is a very low vapour pressure when compared to the other nine substances.

The only measured $LogP_{ow}$ value of 4.35 (European Commission Joint Research Centre, 1996), indicates that TETM is lipophilic. The structure of this substance also supports high (above 3) $LogP_{ow}$ values. TETM is among the more lipophilic substances in this assessment.

Migration

In a study of plasticisers in polypropylene packaging for foods TETM was accidentally found almost half the samples (in the printing ink), but migration was not studied (Nerín et al., 1993).

Migration from PVC to sunflower oil, isooctane or ethanol was 1,280; 1,220 and 450 mg/dm^2 respectively in studies over 1-3 days at the same temperature (Hamdani, Feigenbaum 1996), corresponding to 30-80% of the total TETM amount in the PVC piece. This was approx. twice the migration observed of DEHP. The two PVC samples contained 23.5% DEHP and 27.5% TETM, respectively.

Blood platelet bags, which contained tri-(2-ethylhexyl) trimellitate as a plasticiser, showed that a negligible amount of it leached into calf serum (Chawla et al., 1991).

Use pattern for compound

The main uses of TETM may be in PVC-products used e.g. in the hospital sector, packing, cables, profiles and floor and wall coverings, cf. Table 4.2.

Exposure in work the place

Focus in the EASE-calculation is on the production of cables.

The following assumptions are made with regard to the workplace exposure:

- production takes place at a temperature of 180 °C
- required legal exhaust ventilation is in place
- contact with the substance will only take place incidentally, e.g. in relation to cleaning and maintenance of production equipment.

Possible main exposure routes in the workplace:
- inhalation of vapours.

Based on this scenario, the EASE calculation provides the results shown in Table 5.1.

Table 5.1
Estimated values of TETM in the working environment according to the EASE calculation

Route of exposure	EASE value	Unit
Vapour concentration in air for workers	3-10	ppm
Vapour concentration in air for workers	68.2-227	mg/m^3
Potential dermal uptake for workers	0	mg/kg/day

Consumer exposure

The EASE calculation focus has on use of cables in a normal private house.

Based on this scenario the EASE calculation gives the results shown in Table 5.2.

Table 5.2
The estimated potential daily intake of TETM by consumer according to the EASE calculation

Route of exposure	Daily intake in mg/kg bw/day	Ratio of the ADI
Inhalatory intake	2.16×10^{-16}	*
Dermal uptake	8.04×10^{-21}	*
Oral intake	0	*
Total chronic uptake via different routes	1.62×10^{-16}	*
Total acute uptake via different routes	0	*

*: The ADI has not been established. A Group restriction value of 0.05 mg/kg bw/d based on DEHP peroxisome proliferation data has conservatively been assigned to other dialkyl esters.

Environmental exposure of humans

The amount established in the 'Usage' section is used to calculate exposure for a number of environmental compartments by EU TGD/EUSES. A restriction value of 0.05 mg/kg bw/d (Group R) for food contact materials have been allocated (SCF, 2000) for TETM, and this value is not exceeded according to the EUSES estimates. Furthermore, as an ester TETM may potentially hydrolyse in the gastro-intestinal fluid. Whether this also may occur to some extent in the environment is not clear, and no data is available for TETM on this property.

Table 5.3
The estimated human doses of TETM through intake of water, fish, leaf of crops, roots of crops, meat, milk and air.

TETM		Estimation (~1,800 t)	Worst case (10,700 t)
		mg/kg/d	mg/kg/d
Drinking water		4.6×10^{-8}	2.6×10^{-7}
Fish	BCF estimated*	1.0×10^{-5}	6.0×10^{-5}
Plants			
	Leaf crops	$1. \times 10^{-11}$	8×10^{-11}
	Root crops	4×10^{-10}	2×10^{-9}
Meat		6×10^{-10}	4×10^{-9}
Milk		4×10^{-10}	2×10^{-9}
Air		3×10^{-7}	2×10^{-6}
Total regional		1.0×10^{-5}	6.2×10^{-5}

* Measured BCF value not available

Exposure in the environment

The estimated concentration levels of TETM reflects the low solubility in aqueous solutions combined with the extraordinary high estimated $LogP_{ow}$ and a resulting association with particles (sediment and soils).

Table 5.4
The estimated regional concentrations of TETM in water, soil and air.

Compartment	Aquatic			Terres-trial				Air
TETM	$Surface_t$	$Surface_d$	Sediment	Natural	Agricul-tural	Porewa-ter of agri. Soil.	Industrial	
	mg/l	mg/l	mg/kg	mg/kg	mg/kg	mg/l	mg/kg	mg/m3
Estimation (~1,800 t)	6×10^{-6}	6×10^{-6}	0.00092	2×10^{-10}	9×10^{-8}	4×10^{-10}	8×10^{-7}	1×10^{-6}
Worst case (10,700 t)	4×10^{-5}	4×10^{-5}	0.0054	1×10^{-9}	5×10^{-7}	2×10^{-9}	5×10^{-6}	8×10^{-6}

Secondary poisoning

TETM has an extraordinary high estimated $LogP_{ow}$, which may give rise to high bioaccumulation provided BCF also increases, and consequently a risk of secondary poisoning.

TETM has a potential for secondary poisoning if the evaluation is based on the estimated BCF alone and the estimated $LogP_{ow}$. However, if TETM occurs under acidic or basic conditions a hydrolysis may take place thus cleaving the ester bond producing the trimellitic acid and 2-ethylhexanols. Whether this also may occur to some extent in the environment is not clear, and no data is available for TETM. Trimellitic anhydride formed from the acid at elevated temperature has a range of respiratory effects.

Table 5.5
The estimated regional concentrations of TETM in fish, plants, meat and milk.

Articles of food	Wet fish		Plants			Meat	Milk
TETM	Estimate	measured	Roots	Leaves	Grass		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kgww	mg/kgww	mg/kgww
Estimation (~1,800 t)	0.0063	n/a	8×10^{-8}	8×10^{-10}	0.0001	1×10^{-7}	5×10^{-8}
Worst case (10,700 t)	0.037	n/a	4×10^{-7}	5×10^{-9}	0.0008	9×10^{-7}	3×10^{-7}

5.5.2 Health assessment

Key toxicity data on TETM are presented Table 5.1.

Table 5.1
Selected toxicity data on TETM.

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref. (datasheet)
Acute oral toxicity	Mouse Rat Rat	N.D. N.D. N.D.		LD_{50}>3.2 g/kg bw LD_{50}>3.2 g/kg bw LD_{50}=9.85 g/kg bw	2, 3 1, 3 2
Acute inhalation toxicity	Rat	N.D.	4 hrs	LC_{50}=2.6 mg/l	2, 3
Acute dermal toxicity	Rabbit	OECD 402/1981	24 hrs, covered	LD_{50}=1.97 g/kg bw. No overt clinical signs	2
Acute toxicity, other routes	Rat	i.p.		LD_{50}=3,200 mg/l	2
Irritation - skin	Rabbit	OECD 404/1984	0.5 ml, occlusive, 24 hrs	Slightly irritating	2
- eye	Rabbit	OECD 405/1984	0.1 ml	Slightly irritating	2
- inhalation	Rat	N.D.	230 mg/m^3, 6 hrs	Minimal irritation, no deaths	2
	Rat	N.D.	16 ppm, 6 hrs	Moderate irritation	2
	Rat	N.D.	2640 mg/m^3, 6 hrs	Severe irritation	3
Sensitisation	Guinea pig	OECD 406/1981	0.5 ml, occlusive, 24 hrs, 10 applications	Not sensitising	2, 3
Repeated dose toxicity	Rat (Fisher 344)	Oral	0, 184, 650, 1826 mg/kg bw in diet (28 days).	LOAEL=184 mg/kg bw/day, slightly increased liver weights, slight peroxisome proliferation	2
	Dog	N.D.	14 and 42 mg/kg bw/day injections for 14 days	Increased relative liver and spleen weight in top dose group. LOAEL=42 mg/kg bw/day	2
Genetic toxicity	*Salmonella typhimurium*	Ames test, +/-	N.D.	Not mutagenic	2
	CHO cells	In vitro mammalian cell gene mutation test, +/-	5-200 nl/ml	No chromosome aberration	2
	Rat hepatocytes	HGPRT assay +/-	250-5000 nl/ml	No indication of UDS	2
Reproductive / developmental toxicity	-				
Carcinogenicity	Mouse (A)	N.D.	1,400 mg/kg bw/day	Negative	2
Experience with human exposure	Human	Inhalation	Mist and fumes from hot processing	May irritate eyes, nose, throat and upper respiratory tract	1

References: 1) European Commission Joint Research Centre (1996), 2) European Commission Joint Research Centre (2000), 3) TNO BIBRA International Ltd (1993)

Observations in human	Mist and fumes from hot processing may cause irritation, nausea and vomiting.
Acute toxicity	TETM has been found to be of low acute oral and dermal toxicity in laboratory animals. By inhalation the substance is more toxic and should be classified as Xn (*Harmful);* R20 *(Harmful by inhalation)* according to the classification criteria.
Irritation	TETM has been shown to irritate the skin of guinea pigs, rabbits and mice and the eyes of rabbits (European Commission Joint Research Centre, 2000). TETM has been shown to cause irritation when it is inhaled in rat studies (TNO BIBRA, 1993).
Sensitisation	An attempt to induce sensitisation in 10 guinea-pigs did not show any sign of effect (TNO BIBRA, 1993).
Repeated dose toxicity	Increased weight of liver and spleen were reported in dogs following i.p. exposure for 14 days. LOAEL was 42 mg/kg bw/day (European Commission Joint Research Centre, 2000), In rats 28 days administration of TETM in the diet resulted in slightly increased liver weights and peroxisome proliferation. LOAEL was 184 mg/kg bw/day (European Commission Joint Research Centre, 2000).
Genetic toxicity	TETM is not found to produce any genotoxic effects, and the available data do not indicate that TETM is mutagenic (European Commission Joint Research Centre, 2000).
Long term toxicity	Signs of reproductive toxicity or carcinogenicity were not reported in the available data from laboratory studies. TETM was found to be negative in a cancer study with mouse (European Commission Joint Research Centre, 2000).
NOAEL/LOAEL	The lowest identified LOAEL was 42 mg/kg bw/day following injections in dogs for 14 days and 184 mg/kg bw/day following oral exposure in rats (European Commission Joint Research Centre, 2000).
Summary of known toxicity	TETM has been found to be of low acute oral and dermal toxicity in laboratory animals. The skin of guinea pigs, rabbits and mice can be irritated by TETM, which is also seen to irritate eyes of rabbits. TETM can cause irritation when inhaled by rats. Repeated oral administration of TETM in rats produced slightly increased liver weights and peroxisome proliferation. Repeated injections in dogs resulted in increased liver and spleen weights.
Critical effect	The identified critical effects related to lung changes observed in rats from inhalation of the substance.
Classification	Based on one available inhalation study TETM should be classified Xn *(Harmful)*; R20 *(Dangerous by inhalation)*. Other effects cannot be evaluated properly.

Exposure versus toxicity

A comparison between the calculated exposure of consumers and the available toxicological information about TETM indicates that the selected exposure scenario represents a limited risk to human health. Slight irritation may be expected.

General exposure of the population may occur through dermal contact with consumer products containing TETM and ingestion of contaminated food. Based on the selected scenario, the EASE-calculation indicates that the exposure of TETM in consumers represents very small values and therefore probably constitutes a limited contribution to the overall exposure of consumers.

Concerning exposure in the working environment, exposure may occur through inhalation of dust particles and dermal contact when working at places where TETM is handled. The EASE-calculation indicates that the concentration of TETM in the working environment in relation to the selected scenario can reach levels of up to 227 mg/m^3 and 10 ppm. Rats exposed to 10 times this concentration level have shown minimal irritation, but precautionary measures may be necessary.

5.5.3 Environmental assessment

Generally, data on environmental effects from TETM are not available. Only data on biodegradation are available. In the following the most sensitive data are presented.

Table 5.1
Ecotoxicity and fate data on TETM.

TETM	Aquatic (mg/l)				Terrestrial	Bioaccumulation	Biodegradation (%)	
	Algae	Crustaceans	Fish	Microorganisms			Aerobic	Anaerobic
						BCF	28 days	
Acute	N.D.	>1	>1	N.D.	N.D.	N.D.	14, OECD 301C	N.D.
Chronic	N.D.	0.082 NOEC 21d	N.D.	N.D.	N.D.	-	-	-

N.D.: No data available.

Aquatic and terrestrial ecotoxicity

Very limited data on aquatic ecotoxicity of TETM are available (European Commission Joint Research Centre, 2000), but in these experiments TETM is not acutely toxic at solubility limit. A NOEC from a 21 days chronic experiment is available. No data on terrestrial ecotoxicity were identified.

Bioaccumulation

No BCF data were available, but LogP_{ow} is above three (4.35), and bioaccumulative properties may therefore be expected. The molecular weight is close to 600, which may be assumed to limit the membrane transport and general uptake of the compound.

Aerobic and anaerobic biodegradation

The available data indicates that TETM does not biodegrade readily (European Commission Joint Research Centre, 2000). It should be noted that the conditions of the biodegradation test were not listed in the reference, and it cannot be determined whether the degradation is in reality ready or inherent.

Risk assessment

The data availability is insufficient for calculating PNECs according to the EU TGD, since only two acute tests are available. If, however, it is assumed that a PNEC for water based on e.g. the NOEC/100 is acceptable, the assessment gives the following results (PNEC for water 0.0008 mg/l):

Table 5.2
Risk Assessment on TETM (based on incomplete data set)

Risk assessment	Aquatic	
	$Surface_t$	Sediment
Best guess		
Aquatic	0.0075	0.005
Worst case		
Aquatic	0.05	0.026

Based on the experience with phthalates and the relatively high octanol-water partition coefficient TETM, it may be assumed that the potential for environmental effects is associated with the accumulation of the compound in biota, in aquatic sediments and in soils amended with sewage sludge.

5.6 O-toluene sulfonamide; 88-19-7

5.6.1 Use, emission and exposure

Physical chemical properties

Alkyl sulfone esters are based on phenol, sulphate, and an alkyl chain. The sulfone esters are more resistant toward hydrolysis than other ester based plasticisers.

The available solubility data of o-toluene sulfonamide (OTSA) ranges from slightly soluble in water to 1.62 g/l at 25 °C. OTSA is relatively soluble compared to the other investigated compounds.

OTSA has an estimated vapour pressure 6×10^{-5} at 25 °C, which is one of the highest vapour pressure among the compounds investigated.

Only one measured value $LogP_{ow}$ of 0.84 is available on OTSA (HSDB 2000). The P_{ow} value places OTSA among the least lipophilic compounds investigated here.

Migration

Less than 0.2 mg/kg (detection limit) migrated from package material containing 0.96-3.3 mg/dm^2 to food (Nerín et al., 1993). The OTSA concentration in the packaging material was, however, 100 times lower than for other plasticisers.

Use pattern for compound

OTSA is not used much presently for plasticising purposes, and information has proven difficult to obtain. In the substitution process it is assumed that the main uses of OTSA may be in PVC-cables, cf. Table 4.2.

Exposure in the work place

The EASE-calculation focuses on the production of cables.

The following assumptions are made with regard to the workplace exposure:

- production takes place at a temperature of 180 °C
- required legal exhaust ventilation is in place

- contact with the substance will only take place incidentally, e.g. in relation to cleaning and maintenance of production equipment.

Based on this scenario the EASE calculation provides the results shown in Table 5.1.

Table 5.1
Estimated values of OTSA in the working environment according to the EASE calculation.

Route of exposure	EASE value	Unit
Vapour concentration in air for workers	0.5-3	ppm
Vapour concentration in air for workers	3.56-21.4	mg/m^3
Potential dermal uptake for workers	0	mg/kg/day

Consumer exposure

In the EASE, focus is on the use of cables in a private household.

Based on this scenario the EASE calculation provides the results shown in Table 5.2.

Table 5.2
The estimated potential daily intake of OTSA by consumers according to the EASE calculation.

Route of exposure	Daily intake in mg/kg bw/day	Ratio of the ADI
Inhalatory intake	5.82×10^{-6}	*
Dermal uptake	8.04×10^{-13}	*
Oral intake	0	*
Total chronic uptake via different routes	4.36×10^{-6}	*
Total acute uptake via different routes	0	*

*: The ADI has not been established

Environmental exposure of humans

The EUSES-calculation indicates that humans may by exposed for the substance as illustrated in the following table.

Table 5.3
The estimated human doses of OTSA through intake of water, fish, leaf of crops, roots of crops, meat, milk and air.

OTSA		Estimation (30 t)	Worst case (10,700 t)
		mg/kg/d	mg/kg/d
Drinking water		0.000002	0.000253
Fish	BCF estimated*	2×10^{-7}	2.1×10^{-5}
Plants	Leaf crops	1×10^{-7}	5.2×10^{-5}
	Root crops	2×10^{-8}	5.2×10^{-6}
Meat		2×10^{-11}	2.4×10^{-9}
Milk		3×10^{-10}	4×10^{-8}
Air		1×10^{-10}	5×10^{-8}
Total regional		0.000002	0.000331

* Measured BCF value not available

Exposure in the environment

The estimated concentration levels of OTSA show that concentrations in the aqueous compartment are relatively high compared to other plasticisers due to the high solubility of OTSA.

Table 5.4
The estimated regional concentrations of OTSA in water, soil and air.

Compartment	Aquatic			Terres-trial				Air
OTSA	$Surface_t$	$Surface_d$	Sediment	Natural	Agricul-tural	Porewa-ter of agri. soil	Industrial	
	mg/l	mg/l	mg/kg	mg/kg	mg/kg	mg/l	mg/kg	mg/m^3
Estimation (30 t)	0.0001	0.0001	0.00005	9×10^{-7}	9×10^{-7}	3×10^{-6}	1×10^{-5}	7×10^{-10}
Worst case (10,700 t)	0.0089	0.0089	0.00634	3.1×10^{-4}	3.1×10^{-4}	9.4×10^{-4}	3.4×10^{-3}	2.4×10^{-7}

Secondary poisoning

Due to the high aqueous solubility and low $LogP_{ow}$ the is no indication of risk of secondary poisoning from OTSA.

Table 5.5
The estimated regional concentrations of OTSA in fish, plants, meat and milk.

Articles of food	Wet fish		Plants			Meat	Milk
OTSA	estimate	measured	Roots	Leaves	Grass		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kgww	mg/kgww	mg/kgww
Estimation (30 t)	0.0001	N/A	3×10^{-6}	9×10^{-6}	9×10^{-6}	4×10^{-9}	4×10^{-8}
Worst case (10,700 t)	0.0125	N/A	9.6×10^{-4}	3.0×10^{-3}	3.0×10^{-3}	6×10^{-7}	6×10^{-6}

5.6.2 Health assessment

The key toxicity data on OTSA are presented in Table 5.1.

Table 5.1
Selected toxicity data on OTSA. No data on acute toxicity, irritation, sensitivity or subchronic toxicity were identified.

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Acute oral toxicity	-				
Acute inhalation toxicity	-				
Acute dermal toxicity	-				
Acute toxicity, other routes	-				
Irritation - skin	-				
- eye	-				
Sensitisation	-				
Repeated dose toxicity	-				
Genetic toxicity	*Salmonella typhimurium*	Ames test	N.D	Not mutagenic	2
	Salmonella sp.	Modified Salmonella/microsome test	N.D.	Weak mutagenic effect.	1
Reproductive / developmental toxicity	Rat	N.D. (gavage)	0-250 mg/kg throughout gestation and lactation	Dose-response for bladder calculi in 21-day-old pubs and 105-day old rats. Found to be teratogenic.	1
Carcinogenicity	Rat	N.D. (oral)	N.D.	Limited evidence.	1
	Rat	N.D. (oral)	0, 20 and 200 mg/kg bw. (lifetime)	No increased incidence of malignant tumours.	1
Experience with human exposure*	A 2-month old infant	Oral dose	1,500 mg dose of sulfasalazine (same group as o-toluene-sulphonamide)	No symptoms of toxicity following inadvertent uptake.	1

***** Only information on chemically related products; References: 1) HSDB (2000), 2) Genetox (2000)

Observations in humans

No information regarding OTSA is available. A 2-month old infant did not develop symptoms of toxicity following inadvertent uptake of a 1,500 mg dose of sulfasalazine (same group as o-toluene sulphonamide).

One patient developed seizures, coma, hypoxia, hyperglycemia, metabolic acidosis and methemoglobinemia after an oral dose of 50 mg sulfasalazine and 50 mg paracetamol.

Overdose of sulfasalazine resulted in coma in one patient and tremor in another.

Acute toxicity	Relevant data not found.
Irritation	Relevant data not found.
Sensitisation	Relevant data not found.
Repeated dose toxicity	Relevant data not found.
Genetic toxicity	OTSA is reported to exhibit only weak mutagenic activity (Genetox 2000).
Long term toxicity	OTSA has been reported to be teratogenic in rats (HSDB 2000). This, however, is based on studies without detailed descriptions of the study design. In connection with assessment of saccharine and its impurities, among others OTSA, it has been found that these impurities are responsible for the reproductive effects of impure saccharine. There is limited evidence that OTSA is carcinogenic when administered orally to rats. This has been suggested as the cause of carcinogenicity of saccharin. The available data suggest that OTSA impurities at the levels normally found in commercial saccharin do not contribute to the carcinogenicity of saccharin
NOAEL/LOAEL	No NOAEL or LOAEL has been established.
Summary of known toxicity	O-toluene sulphonamide has been reported to be teratogenic in rats, but only exhibiting a weak mutagenic activity. There is limited evidence that o-toluene sulphonamide is carcinogenic when administered orally to rats.
Critical effect	Based on very limited data the critical effect has been identified as possible teratogenicity observed in rats.
Classification	It is not possible to evaluate the data against the classification criteria for teratogenicity, as information is too sparse. Other described effects are not classifiable.
Exposure versus toxicity	A comparison between the calculated exposure of consumers and the available toxicological information about OTSA indicates that the selected exposure scenario represents a minor risk to human health. General exposure of the population may occur through dermal contact with consumer products containing OTSA and ingestion of contaminated food. Based on the selected scenario, the EASE-calculation indicates that the exposure of OTSA in consumers represents very small values and therefore probably constitutes a limited contribution to the overall exposure of consumers. Concerning exposure in the working environment, exposure may occur through inhalation of dust particles and dermal contact when working in places where OTSA is handled. The EASE-calculation indicates that the concentration of OTSA in the working environment of the selected scenario can reach levels of up to 21.4 mg/m^3 and 3 ppm. Data are not available for comparison.

5.6.3 Environmental assessment

Generally, data on environmental effects from OTSA are not available. Only data on bioaccumulation and biodegradation are available. In the following the most sensitive data are presented.

Table 5.1
Ecotoxicity and fate data on OTSA

OTSA	Aquatic (mg/l)				Terres-trial	Bioac-cumula-tion	Biodegradation (%)	
	Algae	Crusta-ceans	Fish	Microor-ganisms			Aerobic	Anaero-bic
						BCF	28 days	
Acute	N.D.	N.D.	N.D.	N.D.	N.D.	0.4-2.6	0 (14 days)	N.D.
Chronic	N.D.	N.D.	N.D.	N.D.	N.D.	-	-	-

N.D.: No data available.

Aquatic and terrestrial ecotoxicity

No data on aquatic organisms or on terrestrial ecotoxicity of OTSA were available.

Bioaccumulation

The available measured BCF indicate that OTSA do not bioaccumulate (Chemicals Inspection and Testing Institute, 1992). The compound has no potential for bioaccumulation based on the measured $LogP_{ow}$ (0.84).

Aerobic and anaerobic biodegradation

According to the available data OTSA do not biodegradable readily or inherently (Chemicals Inspection and Testing Institute, 1992).

Risk assessment

The data available are insufficient for calculating PNECs or providing other indications of ecotoxicity for the assessment of risk of OTSA.

Based on the physical-chemical properties of OTSA, it must be assumed that the potential for environmental effects is associated with the relatively high aqueous solubility and consequent distribution to the aquatic environment.

5.7 2,2,4-trimethyl 1,3-pentandiol diisobutyrate; 6846-50-0

5.7.1 Use, emission and exposure

Physical chemical properties

Very little or no data is available on production and properties of 2,2,4-trimethyl 1,3-pentandiol diisobutyrate (TXIB).

The solubility data of 1,3-pentandiol diisobutyrate measured at an unknown temperature is 0.001-0.002 g/l. TXIB is relatively insoluble compared to the other investigated compounds.

In the latest edition of IUCLID (2000) an estimated vapour pressure of TXIB is given (0.009), but no unit is reported. An EUSES assessment can not be performed due to an incomplete data set.

Only an estimated value $LogP_{ow}$ of 4.1 based on extrapolation after liquid chromatography is available for TXIB (European Commission Joint Research Center, 2000). The P_{ow} value places TXIB among the more lipophilic compounds investigated here.

Use pattern for compound

The main uses of TXIB may be in the PVC-products used e.g. in the hospital sector, packing, cables, profiles, floor and wall coverings, printing ink and paint/lacquer, cf. Table 4.2.

Exposure in the work place

Sufficient physical-chemical data have not been available to perform an EASE calculation.

It is estimated that part of the production is a calendar/press. This process has been assumed to take place at a temperature of 200 º C and with the legally required exhaust ventilation. It is further assumed that contact with the substance may be extensive due to formation of aerosols during the production.

Based on this scenario, and in recognition of the lack of data concerning health, it may be concluded that TXIB may occur in the working environment in concentrations, which can be of concern. However, there is a need for more information to substantiate this conclusion.

Consumer exposure

The lack of available physical-chemical and toxicological data points at a need for further investigation of the exposure of the substance to consumers.

Exposure in the environment

Insufficient data is available for estimation of environmental concentrations with the EUSES model.

5.7.2 Health assessment

Summary of known toxicity

The key available toxicity data for TXIB are presented in Table 5.1.

Table 5.1
Selected toxicity data on TXIB.

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Acute oral toxicity	Rat	N.D.		LD50 > 3,200 mg/kg bw	1
Acute inhalation toxicity	Rat	N.D.	0.53 or 0.12 mg/l for 6h	LC50 > 5.3 mg/l	1
Acute dermal toxicity	Guinea pig	N.D.		LD50 > 20 ml/kg	1
Acute toxicity, other routes	Rat	N.D. (i.p.)		LD50 approx. 3,200 mg/kg bw	1
Irritation - skin	Guinea pig	N.D.	Covered and uncovered. Dose not mentioned.	Slight skin irritation when uncovered. More irritating when covered.	1
- eye	Rabbit	OECD 405	0.1 ml	Not irritating	1
Sensitisation	Guinea pig	OECD 406	Injection via foot pad. No detailed information	Not sensitising	1
Repeated dose toxicity	Sprague Dawley rats	N.D. (oral)	0.1 and 1 % w/w for 52 or 99 days	NOAEL = 0.1% LOAEL=1% Reversible liver weight change in high dose group	1
	Dog (Beagle)	N.D. (oral)	0.1%, 0.35%, 1% 13 weeks	No significant findings	1
Genetic toxicity	-				
Reproductive / developmental toxicity	-				
Carcinogenicity	-				
Experience with human exposure	-				

References 1) European Commission Joint Research Centre (2000)

Acute toxicity

Acute toxicity has been tested at doses where no effects were observed. Precise LD_{50}-values are therefore not identified ((European Commission Joint Research Centre, 2000).

Irritation

TXIB was observed to be slightly irritating in guinea pigs, especially when covered, but has not been observed to be irritating to rabbit eyes (European Commission Joint Research Centre, 2000).

Sensitisation

Sensitisation has not been observed in the reviewed data (European Commission Joint Research Centre, 2000).

Repeated dose toxicity — In a repeated dose toxicity study in rats reversible liver weight changes were observed in the high dose group (1%) (European Commission Joint Research Centre, 2000).

Genetic toxicity — No data available.

Long term toxicity — No data available.

NOAEL/LOAEL — In a repeated dose toxicity study in rats a NOAEL of 0.1% TXIB in the diet. has been identified. Reversible liver weight changes were observed in the high dose group (1%) (European Commission Joint Research Centre, 2000).

Critical effect — The critical effect based on the available data appears to be the repeated dose toxicity following oral administration in rats.

Classification — It id not possible to conclude about the classification of TXIB based on the available literature.

Summary of known toxicity — The few available data indicate that TXIB is a substance of low toxicity. Results from animal tests do not fulfil the classification criteria with regard to acute toxicity, skin and eye irritation and skin sensitisation. Reversible liver changes were found rats in a chronic study whereas chronic toxicity testing in beagles did not reveal any significant findings.

5.7.3 Environmental assessment

The only available data on TXIB is the estimated $LogP_{ow}$ of 4.1, which indicates that this compound is lipophilic with some potential for bioaccumulation ($LogP_{ow}$ >3).

Only a very limited data set is available on aquatic ecotoxicity for TXIB. No effects were apparently observed in the reported test ranges, and a NOEC (96h) for these acute tests are given as 1.55 mg/l. No information on terrestrial ecotoxicity of TXIB was available.

Aerobic and anaerobic biodegradation cannot be evaluated since no data or incomplete data on TXIB were available.

Table 5.1
Ecotoxicity and fate data on TXIB.

TXIB	Aquatic (mg/l)				Terrestrial	Bioaccumulation	Biodegradation (%)	
	Algae	Crustaceans	Fish	Microorganisms			Aerobic	Anaerobic
						BCF	28 days	
Acute	N.D.	>1.46 LC_{50} (96h)	>1.55	N.D.	N.D.	N.D.	99.9 % at 650 mg/l (incomplete)	N.D.
Chronic	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.

N.D.: No data available.

Risk assessment

The data availability is insufficient for calculating PNECs or providing other indications of ecotoxicity for the assessment of risk of TXIB.

5.8 Epoxidised soybean oil; 8013-07-8

5.8.1 Use, emission and exposure

Physical-chemical properties

Epoxidised soybean oil (ESBO) the dominant plasticiser among the epoxidised oils and is produced by epoxidation of soybean oil. ESBO has a high molecular weight and a spacious molecular structure. These two properties in combination make ESBO more resistant to migration. The high molecular weight and the linear structure of ESBO cause these plasticisers to work less effective at lower temperatures.

The only available data on ESBO is the estimated $LogP_{ow}$ of >6 which indicates that this compound is lipophilic (Syracuse Research Corporation, 2000). When compared to the other investigated substances, the magnitude of the $LogP_{ow}$ value is in the higher end.

Migration

ESBO (used as a stabiliser) showed limited migration from PVC to three lipophilic solvents in the study by Hamdani and Feigenbaum (1996). Typically, approx. half the migration observed for DEHP and less than half compared to TETM. However, in the more polar ethanol ESBO migrate equal to or more than the other plasticisers.

Gilbert et al. (1986) demonstrated that ESBO migrated from PVC bottles to diethyl ether in a 10 days test at 306 mg/dm^2 or 3,492 mg/kg. The ESBO was characterised as ranging from C_{12} to C_{20} with mainly epoxy-oleate (25%) and epoxy-linoleate (52%). Migration of ESBO into three aqueous simulants (water, 50% ethanol and 3% acetic acid) ranged from 0.23 to 0.3 mg/kg.

Levels of ESBO in fresh retail meat samples wrapped in film ranged from less than 1 to 4 mg/kg, but were higher in cooked food and in foods heated in microwave oven (Castle et al., 1990).

The available data on physical-chemical properties does not suffice to establish an EUSES scenario. This is a general problem for mixtures.

Use pattern for compound

The main uses of ESBO may be in PVC-products such as those used in packing, cables, printing ink, paint/lacquer, adhesives and fillers, cf. Table 4.2.

Exposure in the work place

Since ESBO is a mixture of different substances, it is not possible to make an EASE-calculation. As seen in the next section, ESBO may be regarded as only slightly acute toxic by ingestion.

As a worst-case situation involving ESBO in the working environment, professional painting in a room with out ventilation (e.g. a private household) has been selected.

It is concluded that the exposure in the work place is of minor importance, since the substance is mainly toxic by ingestion. Normal hygiene in the working environment, such as washing hands before eating, is sufficient to reduce the exposure.

Consumer exposure

It is not possible to conduct an EASE-calculation on a mixture such as ESBO.

Living in a painted house, which is painted once a year has been assumed to be a worst-case situation.

As the most important toxic feature of ESBO is oral toxicity, living in a painted house is not expected to result in severe effects.

It cannot be excluded that consumers may ingest minor amounts of ESBO during the yearly work with painting in the house. The most sensitive persons may develop effects as described in the following section.

Environmental exposure of humans

Environmental exposure of humans and exposure of the environment cannot be assessed by EUSES or EASE due to lack of data. However, the prominent physical-chemical feature of ESBO is the $LogP_{ow}$, which is relatively high. Exposures from the environment will therefore be expected from particulate phases (soil and sediment) and possibly from biological material.

5.8.2 Health assessment

The most significant toxicity data on ESBO are presented in Table 5.1.

Table 5.1
Selected toxicity data on ESBO.

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Acute oral toxicity	Rat	N.D.	5,000, 21,000 - 40,000 mg/kg bw.	5,000 mg/kg caused dyspnoe and diarrhoea.	1
		N.D.	N.D.	LD50>5,000 mg/kg bw.	1
Acute inhalation toxicity	-				
Acute dermal toxicity	Rabbit	N.D.	Occlusion (24 hours)	LD50>20,000 mg/kg bw	1
Acute toxicity, other routes	-				
Irritation - skin	Rabbit	EPA, Federal reg., Vol 43, No.163	Occlusion (24 hours)	Not irritating	1
- eye	Rabbit	EPA, Federal reg., Vol 43, No.163	0.5 ml instillation	Not irritating	1
Sensitisation	Guinea pig	N.D.	Induction, i.c. injections, re-challenge with patch tests	Not sensitising	1
Repeated dose toxicity	Rat	N.D. (oral)	0.25% and 2.5% 2 years	NOAEL=1.3 mg/kg bw. Slight injury in uterus at 2.5%.	1
	Rat	N.D.	10 g/kg bw. Epoxide no. 14.6 - 111.5 Up to 10 weeks	Slow growth, death in group receiving ESBO with epoxide no.>49.7. E.No. 105-111.5 – severe degeneration of testes.	1
	Rat	N.D. (oral)	1.4 g/kg/ appl., 2 appl. / week 16 months	NOAEL=1.400 mg/kg (effects not mentioned)	1
Genetic toxicity	*Salmonella typhimurium*	Ames test	N.D	Not mutagenic	1
	Mouse lymphoma cell, L5178Y	+/-		Not mutagenic	1
Reproductive / developmental toxicity	Rat	OECD 415 (gavage)	100, 300 and 1000 mg/kg bw. 0-250 mg/kg	NOAEL, parental=1,000 mg/kg bw; NOAEL, offspring=1,000 mg/kg bw. Severe degeneration of testes in animals treated with compound with epoxide no. 105-111.5.	1
		OECD 414 (gavage)	100, 300, 1000 mg/kg bw/d (6. to 15. day of the pregnancy)	Teratogenicity; NOAEL, parental = 1,000 mg/kg bw, NOAEL, F1 offspring = 1,000 mg/kg bw.	
Carcinogenicity	Rat	N.D. (Oral)	<2.5% (1.4 g/kg bw).	No evidence of carcinogenicity.	1
Experience with human exposure	Human	Inhalation		Asthma developed in a worker exposed to vapour from heated polyvinyl chloride film containing ESBO. Challenge with	1

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
				ESBO vapour of unspecified concentration produced asthmatic symptoms within 5 min.	

References: 1) European Commission Joint Research Centre (1996)

Observations in humans

A worker exposed to vapours from heated polyvinyl chloride film containing ESBO developed asthma. Challenge with ESBO vapour of unspecified concentration produced asthmatic symptoms within 5 min (European Commission Joint Research Centre, 1996).

Acute toxicity

In the acute oral tests LD_{50} in rats ranged between 21,000-40,000 mg/kg bw. indicating low acute oral toxicity. Acute dermal toxicity was low as well; LD50<20,000 mg/kg bw (European Commission Joint Research Centre, 1996).

Irritation

ESBO was shown to be not irritating to skin (European Commission Joint Research Centre, 1996).

Sensitisation

Sensitisation has not been observed in the reviewed data (European Commission Joint Research Centre, 1996).

Repeated dose toxicity

ESBO was found to produce slight injuries in uterus of rats in a repeated dose toxicity study (European Commission Joint Research Centre, 1996).

Genetic toxicity

In the reviewed data ESBO has not been seen to be mutagenic (European Commission Joint Research Centre, 1996).

Mutagenicity testing was conducted on two plasticisers commonly used in plastic clingfilm manufacturing, acetyl-tributylcitrate and epoxidized soybean oil. There are no records of mutagenic testing using a bacterial screening method for these two compounds. The two plasticisers were screened using mutant strains of *Salmonella typhimurium*. The tests indicated that they were not mutagenic (Heath & Reilly 1982).

Long term toxicity

Based on the limited available data, ESBO was not found to be a potential carcinogen or to exhibit reproductive toxicity. Severe degradation of testes has been observed with test material characterised by a high epoxide no. (105-111.5) (European Commission Joint Research Centre, 1996).

NOAEL/LOAEL

In a repeated dose toxicity study in rats a NOAEL of 1.3 mg/kg bw. has been identified. At the higher concentration, slight injury in uterus appeared. In reproductive toxicity tests in mouse and rat, the NOAEL for the parental group was 1,000 mg/kg bw and the NOAEL for the F1 offspring were 1,000 mg/kg bw (European Commission Joint Research Centre, 1996).

Critical effect

The critical effect based on the available data appears to be repeated dose toxicity following oral administration and reproductive toxicity.

Classification

The substance is not classifiable based on available data.

Summary of known toxicity

Based on the available data ESBO can only be regarded as slightly acute toxic by oral exposure. A TDI of 1 mg/kg has been allocated from the EU Scientific Committee for Food (SCF, 2000).

5.8.3 Environmental assessment

Generally, some data on environmental effects from ESBO are available, especially from acute aquatic test systems. In the following the most sensitive data are presented.

Table 5.1
Ecotoxicity and fate data on ESBO.

ESBO	Aquatic (mg/l)				Terrestrial	Bioaccumulation	Biodegradation (%)	
	Algae	Crustaceans	Fish	Microorganisms			Aerobic	Anaerobic
						BCF	28 days	
Acute	N.D.	8 (24 hrs)	900 (48 hrs)	>100 (3 hrs)	N.D.	N.D.	78-79 (at 2 or 10 mg/l)	N.D.
Chronic	N.D.	N.D.	N.D.	N.D.	N.D.	-	-	-

N.D.: No data available.

Aquatic and terrestrial ecotoxicity

No data from test following standard methodology were available. All test results are from test with a shorter duration. Despite the shorter test duration ESBO was shown to be toxic (LC_{50}=8 mg/l) to the crustacean *Daphnia magna* in a 24 hours test (European Commission Joint Research Centre, 1996). ESBO could be classified as toxic to crustaceans but a more precise classification is not possible on the basis of the present data.

ESBO was not toxic to the freshwater fish *Leuciscus idus* in a 48 hours acute toxicity test (European Commission Joint Research Centre, 1996).

Bioaccumulation

No BCF data were available. The estimated Log P_{ow} >6 indicate that ESBO is bioaccumulative.

Aerobic and anaerobic biodegradation

ESBO is ready biodegradable according to the results of two standard OECD tests.

Risk assessment

The PNEC for ESBO is 0.008 mg/l based on the available data and an assessment factor on 1,000 (only test results from two trophic levels).

The data availability is insufficient for calculating PEC and therefore no risk assessment of ESBO is possible.

5.9 Dipropylene glycol dibenzoate; 27138-31-4

5.9.1 Use, emission and exposure

Physical-chemical properties

The water solubility of dipropylene glycol dibenzoate (DGD) is 1.5 mg/l at 25 °C. The magnitude of the water solubility of DGD, places this substance in the group of less water soluble among the substances investigated.

DGD has a vapour pressure of 4.7×10^{-7} mmHg at 25 °C, which when compared to the nine other substances is of smaller magnitude.

Only an estimated LogP_{ow} of 3.88 value is available on DGD. The magnitude of this parameter indicates that DGD has lipophilic properties.

Migration

Migration data on DGD has not been identified.

Use pattern for compound

Information on the production and uses of DGD has not been located. The main uses of DGD may be in adhesives and fillers, cf. Table 4.2.

Exposure in the work place

The EASE calculation focuses on the production of adhesives and fillers.

The following assumptions are made with regard to the workplace exposure:

- production takes place at a temperature of 20 °C
- required legal exhaust ventilation is in place
- contact with the substance will only take place incidentally, e.g. in relation to cleaning and maintenance of production equipment.

Based on this scenario the EASE calculation provides the results shown in Table 5.1.

Table 5.1
Estimated values of DGD in the working environment according to the EASE calculation

Route of exposure	EASE value	Unit
Vapour concentration in air for workers	0.5-3	ppm
Vapour concentration in air for workers	7.12-42.7	mg/m^3
Potential dermal uptake for workers	0	mg/kg/day

Consumer exposure

In the calculation in EASE, focus is on normal use of the bathroom in a private household.

Based on this scenario the EASE calculation gives the results shown in Table 5.2.

Table 5.2
The estimated potential daily intake of DGD by consumer according to the EASE calculation

Route of exposure	Daily intake in mg/kg bw/day	Ratio of the ADI
Inhalatory intake	5.82×10^{-6}	*
Dermal uptake	8.04×10^{-13}	*
Oral intake	0	*
Total chronic uptake via different routes	4.36×10^{-6}	*
Total acute uptake via different routes	0	*

*: The ADI is not established

Environmental exposure of humans

The slight lipophilic properties of DGD cause the compound to accumulate in a minor degree in fish. A measured BCF is not available.

Table 5.3
The estimated regional concentrations of DGD in fish, plants, meat and milk.

Articles of food	Wet fish		Plants			Meat	Milk
DGD	estimate	measured	Roots	Leaves	Grass		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kgww	mg/kgww	mg/kgww
Estimation (~200 t)	0.1	N/A	0.007	0.0028	0.0028	8×10^{-6}	2×10^{-6}
Worst case (10,700 t)	1.3	N/A	0.093	0.0051	0.0051	1.03×10^{-4}	3.3×10^{-5}

Exposure in the environment

DGD has lipophilic properties based on an estimated $LogP_{ow}$ and this will tend to distribute the compound to the particulate phases.

Table 5.4
The estimated regional concentrations of DGD in water, soil and air.

Compartment	Aquatic (mg/l)			Terres-trial				Air
DGD	Sur-face$_t$	Surface$_d$	Sediment	Natural	Agricul-tural	Porewa-ter of agri. soil.	Industrial	
	mg/l	mg/l	mg/kg	mg/kg	mg/kg	mg/l	mg/kg	mg/m3
Estimation (~200 t)	0.0004	0.0004	0.02	0.0004	0.003	0.0001	0.007	1×10^{-8}
Worst case (10,700 t)	0.0032	0.0032	0.17	0.0220	0.046	0.0013	0.346	5.8×10^{-7}

Secondary poisoning

No BCF value is available. The $LogP_{ow}$ is relatively high (3.88) and secondary poisoning cannot be excluded. However, if DGD occurs under acidic or basic conditions hydrolysis of the ester bond may take place producing the benzoic acid and diethylene glycol. Whether this also may occur to some extent in the environment is not clear, and no data on hydrolysis is available for DGD.

Benzoic acid occurs in nature in free and combined forms. It has been used over many years as a preservative in foodstuffs in concentrations up to 0.1%. The human intake from natural sources is low compared to the contribution from foodstuffs (Thorup 1999). An ADI has been assigned by FAO/WHO (cf. Thorup, 1999) of 5 mg/kg bw for benzoic acid.

Table 5.5
The estimated human doses of DGD through intake of water, fish, leaf of crops, roots of crops, meat, milk and air.

DGD		Estimation (~200 t)	Worst case (10,700 t)
		mg/kg/d	mg/kg/d
Drinking water		0.00001	0.00009
Fish	BCF estimated*	0.0002	0.0021
Plants			
	Leaf crops	4.80×10^{-6}	8.67×10^{-5}
	Root crops	0.00004	0.00051
Meat		3×10^{-8}	4.4×10^{-7}
Milk		2×10^{-8}	2.6×10^{-7}
Air		3×10^{-9}	1.3×10^{-7}
Total regional		0.0003	0.0028

* Measured BCF value not available

5.9.2 Health assessment

Summary of known toxicity

There is not sufficient data to describe the toxicity of the substance.

Some benzoic acid derivatives will hydrolyse in aqueous solutions, especially in the acidic gastro-intestinal environment. Information regarding this property is not available for DGD. If the ester bonds of DGD are hydrolysed before exposure of humans this would significantly change the toxicological properties. The resulting benzoic acid is a compound well known to man and it is permitted for conservation purposes in food (Thorup, 1999).

5.9.3 Environmental assessment

No data on the environmental effects from DGD are available.

Aquatic and terrestrial ecotoxicity

No data on aquatic and terrestrial ecotoxicity of DGD were available, and there is no information regarding toxicity to microorganisms. Preliminary QSAR estimates by Danish EPA lead to the classification N; R50/53 (May cause long term effects in the aquatic environment).

Bioaccumulation

No BCF data on DGD were available. The estimated Log P_{ow} of 3.88 (Syracuse Research Corporation, 2000) indicate that DGD is potentially bioaccumulative.

Biodegradation

No data were available on aerobic or anaerobic biodegradation of DGD.

Risk assessment

The data availability is insufficient for calculating PNECs or providing other indications of ecotoxicity for the assessment of risk of DGD.

In parallel with case for humans some benzoic acid derivatives will hydrolyse in aqueous solutions, especially in an acidic environment. This would significantly alter the ecotoxicological and fate properties relative to the parent substance. Benzoic acid occurs naturally, e.g. in berries (Thorup, 1999). Information regarding this property is not available for DGD.

5.10 Dioctyl sebacate; 122-62-3

Sebacates are used to impart good low temperature flexibility similarly to adipates and azelates, and generally have the same plasticising properties (Gächter and Müller, 1993).

5.10.1 Use, emission and exposure

Physical-chemical properties

Dioctyl sebacate (DOS) is in fact the ethylhexyl rather than the octyl compound, but is usually referred to as DOS, and this denotion is kept here. DOS has very low water solubility. The data range from 'insoluble' to an estimated 0.35 µg/l. The upper end of the water solubility range places DOS among the most water insoluble substances assessed here.

The estimated log octanol-water partition coefficient of 10 indicates that DOS is a very lipophilic compound when compared to the other substances in this assessment.

DOS has an estimated vapour pressure of 1.0×10^{-7} mm Hg at 25 °C, which is moderate among the investigated substances.

In the same chemical family, dibutyl sebacate exhibits the characteristics of a slightly smaller compound with higher water solubility, a higher vapour pressure, and it will presumably be less lipophilic. For the EUSES calculation DOS has been set at the maximum octanol-water partition coefficient allowed ($LogP_{ow} = 6$) and the lowest possible water solubility.

Migration

A British study of retail food wrapped in plasticised PVC showed considerably higher concentrations of dibutyl sebacate in several food products (76-137 mg/kg) than various phthalate esters, acetyl tributyl citrate and diphenyl 2-ethylhexyl phosphate, which were typically less than 10 mg/kg (Castle et al., 1988b).

Use pattern for compound

The main uses of DOS are anticipated to be in printing ink and adhesives, cf. Table 4.2.

Exposure in work place

The EASE calculation focuses on the production of printing inks.

The following assumptions are made with regard to the workplace exposure:

- production takes place at a temperature of 30 °C
- required legal exhaust ventilation is in place
- contact with the substance will only take place incidentally, e.g. in relation to cleaning and maintenance of production equipment.

Based on this scenario, the EASE calculation provides the results shown in Table 5.1.

Table 5.1
Estimated values of DOS in the working environment according to the EASE calculation

Route of exposure	EASE value	Unit
Vapour concentration in air for workers	0.5-3	ppm
Vapour concentration in air for workers	8.87-53.2	mg/m^3
Potential dermal uptake for workers	0	mg/kg/day

Consumer exposure

In the calculation in EASE focus is on half an hour daily reading of magazine containing printing ink.

Based on this scenario the EASE calculation gives the results shown in Table 5.2.

Table 5.2
The estimated potential daily intake of DOS by consumer according to the EASE calculation

Route of exposure	Daily intake in mg/kg bw/day	Ratio of the 'ADI' (0.05 mg/kg bw/day)[a]
		%
Inhalatory intake	5.82×10^{-6}	5.01×10^{-2}
Dermal uptake	8.04×10^{-13}	1.61×10^{-9}
Oral intake	0	0
Total chronic uptake via different routes	4.36×10^{-6}	8.72×10^{-3}
Total acute uptake via different routes	0	0

[a] The Group restriction value of 0.05 mg/kg bw/d is based on DEHP peroxisome proliferation data (which is considered conservative).

Environmental exposure of humans

The amount established in 'Usage' section is used calculate exposure for a number of environmental compartments by EU TGD/EUSES. The dose is almost completely derived from consumption of root crops. This is due to the extraordinary high $LogP_{ow}$ of DOS leading to accumulation in agricultural soil. No measured data are available for accumulation in plants.

In consideration of the large differences between measured and estimated BCFs, care must be exerted in the interpretation of the actual bioconcentration in the environment and estimates based on high $LogP_{ow}$. This is also even clearer reflected in the roots crop dose. If the group restriction value of 0.05 mg/kg bw/d is applied as an 'ADI', the ratio to 'ADI' is higher than acceptable (almost 1 in 'Estimation', almost 6 in 'Worst case'), and further elucidation is necessary. A TDI of 3 mg/kg bw/d is available for sebacic acid (SCF, 2000). Data are not available to determine whether DOS will hydrolyse when ingested with root crops.

Table 5.3
The distribution of DOS seen in relation to the accepted daily intake.

DOS		Estimation (1,500 t)	Worst case (10,700 t)
		mg/kg/d	mg/kg/d
Drinking water		3.0×10^{-6}	2.2×10^{-5}
Fish	BCF estimate	0.0015	0.011
Plants	Leaf crops	8.1×10^{-6}	0.000058
	Root crops	0.037	0.27
Meat		0.00023	0.0017
Milk		0.00014	0.00098
Air		8.7×10^{-8}	6.2×10^{-7}
Total regional		0.039	0.28

Exposure in the environment

The estimated concentration levels of DOS indicate the expected very low aqueous concentration due to the low solubility, and a high concentration in the particulate phases (sediment and soils).

Table 5.4
The estimated regional concentrations of DOS in water, soil and air.

Compartment	Aquatic (mg/l)			Terres-trial				Air
DOS	$Surface_t$	$Surface_d$	Sediment	Natural	Agricul-tural	Porewa-ter of agri. soil.	Industrial	
	mg/l	mg/l	mg/kg	mg/kg	mg/kg	mg/l	mg/kg	mg/m3
Estimation (~1,500 t)	0.00004	0.00002	0.5	0.3	1.2	0.00011	4.0	4×10^{-7}
Worst case (10,700 t)	0.00030	0.00014	3.3	2.2	8.8	0.00076	28.5	2.9×10^{-6}

Secondary poisoning

DOS has a potential for secondary poisoning if the evaluation is based on the estimated BCF alone and the estimated $LogP_{ow}$. The ADI is exceeded in the worst case scenario, and nearly so in the estimation scenario. The dose is almost completely derived from consumption of root crops. This is due to the extraordinary high $LogP_{ow}$ of DOS leading to accumulation in agricultural soil. No measured data are available for accumulation in plants.

In consideration of the large differences between measured and estimated BCFs, care must be exerted in the interpretation of the actual bioconcentration in the environment and estimates based on high $LogP_{ow}$. However, a dibutyl derivative of sebacic acid has been shown to hydrolyse in the gastrointestinal fluid. Whether this also may occur to some extent in the environment is not clear, and no data is available for DOS. The TDI of sebacic acid (3 mg/kg bw) is 60 times higher than the value for DOS.

Table 5.5
The estimated regional concentrations of DOS in fish, plants, meat and milk.

Articles of food	Wet fish		Plants			Meat	Milk
DOS	estimate	measured	Roots	Leaves	Grass		
	mg/kg	mg/kg	mg/kg	mg/kg	mg/kgww	mg/kgww	mg/kgww
Estimation (~1.500 t)	0.92	n/a	6.8	0.0005	0.0005	0.54	0.017
Worst case (10,700 t)	6.58	n/a	48.5	0.0034	0.0034	0.39	0.122

5.10.2 Health assessment

The most significant toxicity data on DOS are presented in Table 5.1.

Table 5.1
Selected toxicity data for DOS..

Toxicology	Species	Protocol	Dose levels / duration	Results	Ref.
Acute oral toxicity	Rat	N.D.		LD_{50}=1,280 mg/kg bw.	4
Acute inhalation toxicity	Rat	N.D.	250 mg/m^3 for 4 hours	No adverse effects observed	1
Acute dermal toxicity	-				
Acute toxicity, other routes	Rat Rabbit	N.D. (i.v.) N.D. (i.v.)		LD_{50}=900 mg/kg bw. LD_{50}=540 mg/kg bw	4
Irritation - skin	N.D.	N.D.	N.D.	Not irritating, not absorbed through skin.	2
- eye	-				
Sensitisation	-				
Repeated dose toxicity	Rat	N.D. (inhalation study)	250 mg/m^3 for 4 hrs/d, 5 d/week, 13 weeks	No adverse effects observed	1
	Rat (♂)	N.D. (oral)	1 g/kg bw/day 3 weeks	Increased liver weight, peroxisome proliferation, increased levels of peroxisome enzymes	1
Genetic toxicity	*Salmonella typhimurium*	Ames test	N.D	Not mutagenic	3
Reproductive / developmental toxicity	Rat	N.D. (oral)	10 mg/kg bw/day (19 months)	No effects observed	2
Carcinogenicity	Rat	N.D. (oral)	10 mg/kg bw/day (19 months)	No effects observed	2
Experience with human exposure	Human	-	60 mg/m^3; 1 min Inhalation	Reported threshold of irritant action on mucous membranes of upper resp. tract and eyes.	1
	Humans	-	48 h covering and patch test	No effects observed	1

References: 1) BIBRA (1996), 2) HSDB (2000), 3) CCRIS (2000), 4) NTP (2000)

Observations in humans

Volunteers did not produce signs of irritation or sensitisation during a 48 hours covering and patch test (BIBRA, 1996).

DOS aerosols have been used to demonstrate particle deposition in lungs and respiratory tract, apparently without producing overt toxic effects.

Exposure to 60 mg/m^3 for 1 minute is reported to be the threshold of irritant action on the mucous membranes of the upper respiratory tract and eyes. No further details are available (BIBRA, 1996).

Acute toxicity	The oral LD_{50} for rats is found to be relatively low equal to 1,280 mg/kg bw (NTP, 2000). No adverse effects were observed when rats were exposed to a concentration of 250 mg/m^3 for 4 hours.
Irritation / Sensitisation	Exposure to DOS did not cause irritation or sensitisation on skin in human volunteers during 48 hours covering and patch tests (HSDB 2000).
Repeated dose toxicity	Adverse effects were also not seen in a 13 weeks study where 12 rats were exposed to 250 mg/m^3 for 4 hours per day, 5 days a week (BIBRA, 1996).
Genetic toxicity	DOS was not found to be mutagenic in Ames test.
Long term toxicity	Rats fed a diet containing 10 mg/kg bw for up to 19 months did not show any carcinogenic effects and the reproduction was normal in a 4 generation study of rats fed about 10 mg/kg bw (HSDB 2000).
NOAEL/LOAEL	A NOAEL or LOAEL has not been established, but a dose 10 mg/kg bw did not produce any carcinogenic effects or reprotoxic effects in 19 month feeding studies in rats (HSDB 2000).
Critical effect	The critical effect based on the available data is the acute toxic effect following oral administration.
Classification	The critical effect based on the available data is the acute toxic effect observed in rats following oral administration. Effects include reduced coordination, laboured breathing and diarrhoea, with tissue damage in the liver, spleen, brain and heart (Bibra 1996).
Summary of known toxicity	DOS exhibits moderate acute toxicity when administered orally to rats and fulfils the criteria for classification as harmful if swallowed. The substance does not seem to be an irritant or a sensitiser. Repeated oral administration to rats showed effects on the liver but no signs of carcinogenicity or reproductive toxicity were seen in rat studies.
Daily intake	The EU's Scientific Committee for Food has defined a group restriction for DOS and other dialkyl esters equal to 0.05 mg/kg bw/day (SFC 2000).
Exposure versus toxicity	A comparison between the calculated exposure of consumers and the available toxicological information about DOS indicates that the selected exposure scenario represents a minor risk to human health. General exposure of the population may occur through dermal contact with consumer products containing DOS and ingestion of contaminated food. Based on the selected scenario, the EASE-calculation indicates that the exposure of DOS in consumers represents for some routes very small values and therefore probably constitutes a limited contribution to the overall exposure of consumers. However the inhalation of the product represents a relatively high ratio of the daily intake at a level (0.05%). As seen in Table 5.1 this means that the intake of fish and root crops might be of concern. Concerning exposure in the working environment, exposure may occur through inhalation of dust particles and dermal contact when working in places where DOS is handled. The EASE-calculation indicates that the con-

centration of DOS in the working environment of the selected scenario can reach levels of up to 53.2 mg/m^3 and 3 ppm.

5.10.3 Environmental assessment

Table 5.1
Ecotoxicity and fate data on DOS.

	Aquatic (mg/l)				Terrestrial	Bioaccumulation	Biodegradation (%)	
	Algae	Crustaceans	Fish	Microorganisms			Aerobic	Anaerobic
						BCF	28 days	
Acute	N.D.	N.D.	N.D.	N.D.	N.D.	45,000	N.D.	N.D.
Chronic	N.D.	N.D.	N.D.	N.D.	N.D.	(estimate)	N.D.	N.D.

Aquatic and terrestrial ecotoxicity

No data on ecotoxicity has been identified for DOS or dibutyl sebacate. Sebacic acid is generally considered relatively safe (see 'secondary poisoning'), but no data on hydrolysability is available. Aquatic or terrestrial PNECs cannot be calculated with basis in data on DOS.

Bioaccumulation

Only an estimated BCF is given indicating high bioaccumulation potential (Syracuse Research Corporation, 2000).

Aerobic and anaerobic biodegradation

The high lipophilicity of DOS and other sebacate plasticisers will generally lead to low bioavailability to microorganisms in STP. The biodegradation of phthalate esters is relatively slow due to a lag phase, but complete mineralisation is possible under anaerobic conditions (Kleerebezem et al., 1999).

Risk assessment

The data availability is insufficient for calculating PNECs or providing other indications of ecotoxicity for the assessment of risk of DOS or dibutyl sebacate.

Based on the experience with phthalates and the physical-chemical properties of DOS, it must be assumed that the potential for environmental effects is associated with the accumulation of the compound in biota, in aquatic sediments and in soils amended with sewage sludge.

5.11 Polyester (polyadipates)

Physical-chemical properties

Polyester plasticisers are polymers based on divalent acids, such as adipic, sebacic or azelaic acid (some times also on phthalic acid) condensed with diols. The polycondesation reaction yields a more or less broad molecular weight distribution of the polyester plasticiser, and the end product will display an average molecular weight, which is specific for the individual polymer. Typically, the polyester is a polymer with a molecular weight between 850 and 3500 (Gächter, Müller 1993).

Migration

The polyesters of high viscosity have a good resistance to hydrocarbons, and primarily due to their high molecular weight they show little tendency to migration (Castle et al., 1988a).

Exposure

Due to the chemical nature of polyester plasticisers, the substance data (e.g. a specific molecular weight) required for a quantitative estimate of distribution and concentration by models are not available.

Human health assessment

A polyester based on adipic acid and 1,2-propanediol is frequently used in plasticising PVC, and has been suggested for the assessment. The EU Scientific Committee for Food has a range of polyesters of adipic acid, azelaic acid and various diols in their Synoptic list regarding substances in food contact materials (European Commission, 2000). Limited studies based on a polyester (end capped with fatty acids) are quoted, and a group TDI of 0.5 mg/kg bw/d has been allocated.

The parent compounds adipic acid and 1,2-propanediol have been considered by the same committee in food contact materials. Human health ADI of 5 mg/kg bw/d has been allocated to adipic acid and an ADI of 25 mg/kg bw/d allocated to 1,2-propanediol.

Environmental assessment

No data on the polymer has been identified for the environmental assessment.

Comparing polyester plasticisers with the lower molecular weight parent substances will lead to the following generalised pattern. The polyester will have

- little bioavailability (MW >> 600)
- low volatility
- high tendency to bind to particles
- low or insignificant biodegradability

Risk assessment

All in all, the above characterises an inert substance in the environment, which will not enter the biosphere until the polymeric structure begins to break. Thus, if these substances do not release large quantities of mono- or oligomers, the possible effects should be associated with very long-term exposure or accumulation. Information on this issue has not been identified.

The high molecular weight of the substances places polyester plasticisers are in a borderline area approaching the polymer materials with respect to the evaluation of risk to man and environment.

6 Health and environmental assessment for materials

Polymers may be divided into two categories defined by their chemical structure (OECD 1998):

Thermoplastic polymers are melted or softened in order to be formed under pressure into the required shape, which is established on cooling the product. The process is reversible and the plastics materials can be reshaped and reused. Polyethylene (PE) is a thermoplastic polymer.

Thermosetting resins are converted into finished products with the application of heat and pressure. Chemical cross-linking takes place and the process is not reversible. The materials cannot readily be recovered and reused. Polyurethane (PU) is a thermosetting polymer.

Such properties may have implications in a recycling process e.g. allowing only downcycling. However, the problems associated with these aspects, and the risks associated with production processes for the polymers, the energy consumption or the use of specific (perhaps undesired) chemicals in the production process are not part of the evaluation.

The evaluation of materials is directed toward a comparison with the properties found for the chemicals proposed as substitutes for phthalates in PVC. Being polymers PU and PE and cannot be assessed by the ordinary tools for health and environmental assessment of chemicals. A different approach is used, where migration of mono- or oligomers is considered and their potential for effects are evaluated. The polymer itself is considered in a general assessment. Polymers most often contain various additives, such as pigments, extenders, slip agents, antioxidants etc.

Both PU and PE are already used extensively in the society and the use considered here is therefore an addition to the existing exposure to the polymers. The choice of exposure scenarios is directed toward maximum human contact at the consumer level. There will be given no assessment of the combined load of PU respectively PE to humans or to the environment from the total use of the polymers.

6.1 Polyurethane

PU is assessed through the monomer methylene diphenylene diisocyanate (MDI). In the applications where PU may be a substitute for flexible PVC (e.g. water proof clothing), PU will most likely be based on MDI. This PU is a thermoset plastic formed in a step growth process.

6.1.1 Use, emission and exposure

Physical-chemical properties

MDI in commercial form typically exists as a mixture of the 4,4'-MDI (monomer) and various oligomers of MDI. The commercial mix has CAS no. 9016-87-9 and the 4,4'-monomer has no. 101-68-8. The content of monomeric MDI generally is between 45% and 65 % on a w/w basis. The monomer is rarely separated from the mixture, which typically contains 50% monomer and 50% trimers and higher oligomers (US EPA 1998). This composition, which is very similar to that used in the workplace, renders the

material semisolid and suitable for aerosol generation. Monomeric MDI is formed as a by-product of PMDI synthesis and is rarely separated from the mixture except in special-use applications. The exact composition of monomeric MDI in a mixture likely varies with the manufacturer. Any change in the monomeric composition is expected to be compensated by an increase or decrease in oligomer content.

Monomeric MDI is a solid at room temperature whereas the PMDI mixture is a viscous liquid at room temperature and the vapour pressure is extremely low, about 2 x 10^{-6} kPa at 20 °C of both mixture and MDI (US EPA 1998). Vapour pressure of MDI according to Swedish Chemicals Inspectorate (1994) is 0.003 kPa at room temperature.

Theoretically, isocyanates hydrolyse readily to amine and carbonate moieties. This hydrolysation may, however, also lead to methylene dianiline according to Gilbert (1988), but no data is presented. Monomeric MDI solidifies to a hard crust upon contact with soil or water, if spilled in the pure form. The polymeric mixture has a density larger than water's and will sink without being finely dispersed (Gilbert 1988).

The fate of MDI under test conditions in Salmonella test has been studied. A rapid disappearance was observed in test media, 28% and 0.3% remaining in solution after 45 seconds depending on the co-solvent. A slight increase in the concentration of the aniline degradation product diaminodiphenyl methane occurred (up to ~3%). In distilled water 95% remained (Seel et al 1999).

Migration

No data on migration of monomer MDI from PU has been identified. Isocyanates belong to a chemical family of high reactivity with biological functional groups, such as hydroxyl, amine, and sulfhydryl groups (US EPA 1998).

After loss of MDI from products to air, soil or water exposure of humans or the general flora and fauna in the environment is not expected. The reactivity of the monomer will presumably lead to binding of MDI to abiotic dissolved or particulate organic material before interaction with biota. The complexes are typically not bioavailable and no exposure takes place. After spraying with commercial mix and consequent loss to the atmosphere in a working environment no unreacted MDI was found on filters, only urethane and MDI-urethane (US EPA 1998).

Use pattern for compound

The main use of PU as substitute for PVC-products is anticipated in the waterproof clothes, shoes, boots and waders (see section 4.3.2).

Exposure in the work place

The vapour pressure of MDI at room temperature is less than 10^{-5} mmHg. Due to the low vapour pressure at room temperature, only negligible amounts of MDI vapours are expected to be released into the environment during normal application, e.g. by roller coating, brushing or curtain coating of products containing MDI and when using such products in the form of fillers or joint sealants. Experience gained in monitoring the air during application of MDI-based coatings shows that the concentrations, which from under these conditions are below the occupational exposure limit (0.05 mg/m^3) provided that there is a minimum of air circulation.

Monitoring of MDI concentrations must however be accorded particular attention. Especially when spraying MDI-based formulations or when working at high temperatures, e.g. exposure to sunlight or coating of heated

surfaces. Under such conditions, concentrations of MDI aerosols for exceeding the occupational exposure limit can be formed, either by mechanical means or by recondensation of MDI vapours which are supersaturated at room temperature. At high application temperatures, the vapour pressure and the saturation concentration of MDI increase considerable (Bayer, 1996). Based on information in OECD (1998) for the UK, PU is processed in closed systems.

Consumer exposure

It is not possible to conduct an EASE-calculation on a polymer such as PU. The exposure of consumers may be associated with the release of MDI and oligomers from the polymer. However, no data on migration has been identified.

Environmental exposure of humans

It is not possible to conduct an EUSES-calculation on a polymer such as PU. The exposure of humans from environmental sources may be associated with the release of MDI and oligomers from the polymer. However, no data on migration has been identified.

6.1.2 Health assessment

Observations in humans

Exposure to isocyanates is a leading cause of occupational asthma worldwide. High exposure concentrations, such as might occur during a spill, are a likely risk factor in human sensitisation.

In a cross-sectional study, MDI-induced sensitisation was evaluated in 243 PMDI/MDI foam workers in a 3-year-old facility in which air levels were monitored continuously be area monitors for 24 h per day, during which time the air levels never exceeded 5 ppm. The average duration of employment was 18.2 months. Three cases of occupational asthma were identified, one of which was attributable to a spill.

The available human data concerning occupational exposure to PMDI/MDI, coupled with lack of knowledge about mechanism of action and the possible role of genetic predisposition are insufficient to identify exposure conditions and scenarios responsible for the isocyanate-induced sensitisation.

In a retrospective cohort, mortality and cancer incident study involving 4,154 workers employed at any of nine Swedish polyurethane manufacturing plants, the association between excess cancer deaths or excess deaths from destructive lung diseases was investigated. Workers were exposed to both TDI and MDI. Exposure levels to MDI were normally below the detection limit of the analytical method (<0.01 mg/cm^3) and nearly all were below 0.1 mg/m^3. At the 10% level of significance, no statistically significant association was formed between all-cause cancer and diisocyanate exposure using any of five exposure measures, or for non-Hodkin's lymphoma and rectal cancer (five cases).

Acute toxicity

The LC_{50} in rats has been estimated at 178 mg/m^3 in rats. An LD_{50} in rats of 9,200 mg/kg is reported corresponding to low acute toxicity by ingestion.

Irritation

MDI causes irritation of skin and development of rashes by contact. Exposure to vapours and aerosols irritates eyes, nose, throat and lungs causing coughing, wheering, chest tightness and/or shortness of breath.

Sensitisation

MDI may produce skin sensitisation and allergic symptoms like redness, swelling and inflammation.

An impairment of pulmonary function and induction of sensitisation of the respiratory tract are generally observed when a MDI concentration of 0.2 mg/m^3 (vapours, aerosols) is exceeded. These effects are believed to be no more frequent in exposed persons than in non-exposed control persons, if a maximum air concentration of 0.1 mg/m^3 is maintained.

Allergic sensitisation usually develops after months of exposure.

Asthma characterised by bronchial hyperreactivity, cough, wheeze, tightness in the chest and dysnea, was observed in 12 of 78 foundry workers exposed to MAI concentrations greater than 0.02 ppm (0.2 mg/m^3). Inhalation provocation tests in 6 out of 9 of the asthmatics resulted in specific asthmatic reaction to MDI.

Repeated dose toxicity

In a subchronic toxicity study (range finding) rats were exposed to PMDI aerosol in concentrations of 4, 8 or 12 mg/m^3 for 6h/day, 5 d/week for 13 weeks. Severe aspiratory distress, degenerative lesions in the olfactory epithelium of the nasal cavity and mortality was observed at the highest close level. Histo-pathological lesions of the lungs were also observed in the 8 mg/m^3 dose group suggesting impaired lung clearance. This study demonstrated adverse effects in the lungs and nasal cavity at levels of 4 mg/m^3 and above. However, because of lack of data on aerosol sizes, a quantitative LOAEL could not be derived.

Genetic toxicity

MDI yielded mixed results in genotoxicity tests. Technical grade MDI was positive in the salmonella reverse-mutation plate-incorporation assay in strains TA 98, TA100 in the presence of metabolic actuation and negative in TA1537 at concentrations of up to 100 μg/plate. Conflicting findings are however observed with strains TA98 of TA100. This may partly be attributed to the instability of MDI in DMSO.

Genotoxic metabolic reaction products of MDI have been identified. Free MDA (methylene dianiline) and AMD (N-acetylmethylene dianiline) have been detected in e.g. urine. The level of AMD was about three times higher than that of MDA. MDA is a known animal carcinogen.

Long term toxicity

According to IARC, MDI is classified as Group 3: The agent is not classifiable as to its carcinogenicity to humans.

The results of a two-year inhalation study in rats using aerosols of PMDI revealed a carcinogenic potential. These observations have however been discussed as a result of the irritant effect of the high concentrations of aerosols to which the rats were exposed.

In the cancer bioassay, rats were whole-body exposed to aerosols of PMDI for 6h/d, 5d/w for 24 months in concentrations of 0, 0.2, 1.0 and 6.0 mg/m^3. A NOAEL of 0.2 mg/m^3 and a LOAEL of 1.0 mg/m^3 for respiratory tract effects in both the pulmonary and extrathoracic regions were identified. Although there were no compound-related nasal tumours solitary pulmonary adenomas, described as rare in Wistar rats, were observed. Only one pulmonary adenocarcinoma was observed in one male exposed to 6 mg/m3. Although the study provides evidence of a tumourigenic response to treatment, the significance of only one pulmonary adenocarcinoma is insufficient to distinguish PMDI as an animal carcinogen.

Prenatal toxicity was evaluated in a study with pregnant Wistar rats exposed to respirable PMDI in concentrations of 1, 4, and 12 mg/m^3 for 6h/d from

day 6 to day 15. Statistically, significant effects were observed at the high dose level, effects, which may be a result of maternal toxicity. The study identified a maternal NOAEL at 4 mg/m^3 and a developmental LOAEL of 12 mg/m^3. The study suggests that the potential of PMDI to cause prenatal toxicity and teratogenic effects in this strain is low.

In another developmental study where Wistar rats were whole-body exposed to aerosols of MDI in concentrations of 1, 3 and 9 mg/m3 for 6h/d from day 6 to 15, the NOAEL for developmental effects was identified at 3 mg/m^3.

NOAEL/LOAEL

Lowest reported LOAEL in the available literature was 1.0 mg/m^3 for respiratory tract effects in a chronic study. A NOAEL of 0.2 mg/m^3 in the same study was identified.

Summary of known toxicity

Exposure to MDI has been shown to cause irritation and occupational asthma in humans. Skin sensitisation has been observed as well. Impairment of pulmonary function is also observed.

Sensitisation from low-level exposure is not described.

MDI is classified in Group 3 by IARC: The agent is not classifiable as to it's carcinogenicity to humans. Positive tumourgenic response to treatment has however been shown in a two-year rat study. Findings were not significant.

Conflicting results in Ames mutagenicity tests have been reported.

Exposure of pregnant rodents to MDI has not been shown to cause prenatal effects.

6.1.3 Environmental assessment

Aquatic and terrestrial ecotoxicity

Data quoted from other studies in Gilbert (1988) reportedly show that MDI is virtually non-toxic to crustaceans and fish as tested with a series of standard OECD tests. A result from a 24 hours test on reproduction in crustaceans is reported as no effect at the highest concentration (10 mg/l). The original data are not available. In an experiment with a simulated spill of MDI in marine water the concentration after one day had fallen to 5% of the initial value (Brockhagen, Grieveson 1984), however, zooplankton organisms were reduced in numbers. The same authors report a study showing that mortality in 0.001% MDI over 35 days was 7 of 8 animals.

In comparison acute toxicity of toluen-2,4-diisocyanate to freshwater fish ranged from 165-195 mg/l on exposures from 24 to 96 hours (Curtis et al. 1979). No significant mortality was observed in exposure of saltwater fish up to 500 mg/l.

Biodegradation

Aerobic biodegradation is reported as 'None' in the OECD test for inherent biodegradability (Gilbert 1988). No data was reported for anaerobic biodegradation.

Table 6.1
Ecotoxicity and fate data on MDI

MDI	Aquatic (mg/l)			Microorganisms	Terrestrial	Bioaccumulation	Biodegradation (%)	
	Algae	Crustaceans	Fish	EC_{50} 24h			Aerobic	Anaerobic
			LC_0			BCF	28 days	
Acute	N.D.	> 1,000	> 1,000	> 50	N.D.	N.D.	None (Inherent test)	N.D.
Chronic	N.D.	>10 (LC_0 – 24h)	N.D.	N.D.	N.D.	-	-	-

N.D.: No data available.

Bioaccumulation

Bioaccumulation data have not been identified for MDI or for the PU. The reactivity (and polarity) of MDI makes the use of equilibrium distribution models unsuitable for prediction of bioaccumulation. For the PU polymer as such the average molecular weight is above the value of 600-1000 considered a maximum for uptake in living organisms.

Risk assessment

The risks of significant release of MDI from PU polymer leading to acute effects in the environment seem highly unlikely. Although the data on chronic effects is incomplete, the risks to the environment based on these limited data set seem limited.

6.2 Polyethylene (PE)

PE is a thermoplastic produced from ethylene as an addition or chain growth polymer. It is commercially available in two main forms: high and low density polyethylene (H and LDPE). The former is an almost linear polymer both rigid and hard.

LDPE is branched leading to a more spacious compound and lower density polymer. LDPE substitutes flexible PVC as such, and not only the phthalate plasticiser of the PVC. The assessment evaluates the LDPE material and although PE may be added various substances, e.g. antioxidants (Wessling et al 1998,), the additives are not included in the assessment.

Polyethylene and LDPE has the same CAS no. 9002-88-4.

6.2.1 Use, emission and exposure

Physical-chemical properties

The polymer has a melting point of 130-145 C and a density of 0.92. No information on vapour pressure or $LogP_{ow}$ are available. The average molecular weight ranges from 100.000 to 500.000 depending on the application.

Migration

There is no data available on migration of base monomers or oligomers. The monomer ethylene is a highly volatile chemical and if present in the crude formulation it will evaporate quickly from the polyethylene matrix. Typically, the production process (a chain growth reaction) is also ended with capping of the ends of the chains. There is very limited reaction with the polymer, which is also treated with additives such as antioxidants to avoid the introduction of reactive groups in the polymer skeleton leading to a less stabile material. Thus, no migration is anticipated.

Use pattern for compound

LDPE has to some extent already substituted PVC used in flexible toys. It is expected that a major part of PVC application can be substituted with LDPE products. In the substitution matrix all flexible PVC in toys is converted to LDPE.

Exposure in the work place

PE is produced from ethylene and for (Linear) LDPE also variable amounts of higher alkenes depending on the branching. LDPE is produced in closed systems, but processed in both opened (88%) and closed systems (12%), based on data for the UK (OECD 1998).

Typically, PE granules are heated to 160-260 °C before processing into shape. If excessive heat is applied thermooxidation may take place above 360 °C and aldehydes of short chain alkanes can be formed. These may irritate the respiratory tract.

Consumer exposure

It is not possible to conduct an EASE-calculation on a polymer such as LDPE. It is anticipated that mouthing of LDPE toys by children will be a primary exposure route. A considerable recovery of the volatile alkenes takes place in production (Danish EPA 1995) and it is not expected that consumer products will contain monomers.

Environmental exposure of humans

No environmental exposure to LDPE or it's monomer is anticipated from the polymer due to the apparent lack of migration potential. Ethylene occurs naturally, and is also used in small amounts to ripen fruit and vegetables.

6.2.2 Health assessment

No toxicity data on LDPE are available.

Observations in humans

The massive production of ethylene and polyethylene and the general use of the polymer over the past several decades indicate that exposure of workers and the general population is common. In addition, medical use (e.g., for intrauterine contraceptive devices) has been extensive.

Acute toxicity

No data on LDPE has been identified.

Irritation/sensitisation

Relevant data were not found.

Repeated dose toxicity

Relevant data were not found.

Genetic toxicity

Relevant data were not found.

Long term toxicity

There is no information on LDPE, except for carcinogenicity of implants, which the IARC classification is 'Organic polymeric materials as a group are *not classifiable as to their carcinogenicity to humans (Group 3)*'. The base chemical ethylene is 'not classifiable as to its carcinogenicity to humans (Group 3)' (IARC 1998).

NOAEL/LOAEL

Relevant data were not found.

Summary of known toxicity

Incomplete information is available for an assessment. As a reflection of the general recognition of low toxicity no limit value exist for working environment for the base chemical ethylene although considerable amounts is used (Danish EPA 1995).

6.2.3 Environmental assessment

Aquatic and terrestrial ecotoxicity

No toxicity data for aquatic or terrestrial organisms have been identified. The lack of biological availability due to the high molecular weight of

LDPE indicates that the unbroken polymer itself will not have direct toxic effects in the environment.

Aerobic and anaerobic biodegradation

There is no data identified for biodegradation. However, LDPE is often referred to as a non-degradable polymer, and the primary environmental concern (visible pollution) is associated with lack of degradability.

Bioaccumulation

Bioaccumulation data have not been identified for LDPE. The large molecular weight (100,000-500,000) of the polymer is above the value of 600-1000 considered a maximum for uptake in living organisms.

Risk assessment

The lack of information precludes an assessment of the risk to the environment based on test data or calculation of predicted environmental concentrations. The characteristics of LDPE are those of an inert substance in the environment, which will not enter the biosphere until the polymeric structure begin to break. Thus, as LDPE do not release large quantities of mono- or oligomers, the possible effects would be associated with unknown long-term exposure or accumulation. Possible effects associated with the existence of fibres and polymers under slow degradation in the environment have not received the same intense investigation as the effects associated with the chemical substances.

PE is generally considered one of the least problematic plastics, and no indications of toxicity associated with the polymer have been identified from authorities, industry or NGOs. Environmental or health problems are only described in relation to synthesis of the polymer (energy consumption, base chemicals etc.), which is beyond the scope this evaluation.

7 Combined Assessment of Use, Exposure and Effects

7.1 Chemical Hazard Evaluation

7.1.1 Data availability

Data pattern

The data availability is very variable among the suggested alternatives for phthalate plasticisers and materials. A majority of information is collected based on the CAS number of the suggested compound. For DEHA, ATBC, TEHPA and TETM information is available covering a range of results from tests on toxicological and ecotoxicological properties. However, only DEHA can be considered adequately covered, although some areas need further investigation.

DEHPA, OTSA, TXIB, ESBO, DGB and DOS are covered in less detail, either because of lack of information or because of inferiour quality of the tests. For the substance polyadipate no CAS number is available and information has been searched in bibliographic databases. For this substance no information has been located. A similar lack of data is seen for LDPE. However, the MDI base for PU is well described.

The type of data that are missing varies between compounds. Typically missing data on the environment side are biodegradation data and measured bioaccumulation data. On the health side a less clear pattern is observed, although adequate studies on long-term effects, e.g. reproductive toxicity studies are often lacking.

Data sources

The sources of the data are given primarily in the data sheets in the report appendix and for core information also in the main report. The information includes peer reviewed original papers, databases, previous reviews and reports, books, and proprietary information from suppliers.

It has been attempted to prioritise studies performed after standard test methods and guidelines for inclusion. In a number of cases the database IUCLID (European Commission Joint Research Center, 1996 and 2000), which contains information submitted by the industry, is almost the sole data source (e.g. TXIB). Again standardised tests have been selected whenever possible.

Attention is drawn to the fact that the majority of data are evaluated on the basis of databases on physical-chemical, toxicity and ecotoxicity studies. Although the studies as a rule are reviewed before inclusion in the databases the quality cannot be guaranteed *a priori*, nor is it possible to scrutinise the testing conditions of the original studies. Especially, for older studies the relation to modern guideline based experiments can be difficult to assess and consequently compliance with e.g. classification criteria may not be obvious.

7.1.2 Physical-chemical data

The available data show that none of the substances display hazardous physical-chemical properties, such as flammability etc. The typical substance has low water solubility and a moderate to high lipophilicity ($LogP_{ow}$

4 and higher). Vapour pressures are generally low (a tentative grouping is shown in Table 7.1).

Table 7.1
Relative volatility of substances suggested as alternative to phthalates in PVC. Tentative estimates for substances for which data is not available are given in parenthesis. DEHP is included for comparison.

		Low		Medium		High
Name	CAS no.					
Diethylhexyl adipate	103-23-1			DEHA		
O-acetyl tributyl citrate	77-90-7				ATBC	
Di(2-ethylhexyl) phosphate	298-07-7			DEHPA		
Tri(2-ethylhexyl) phosphate	78-42-2			TEHPA		
Tri-2-ethylhexyl trimellitate	3319-31-1	TETM				
O-toluene sulfonamide	88-19-7					OTSA
2,2,4-trimethyl 1,3-pentandiol diisobutyrate	6846-50-0			(TXIB)		
Soybean oil epoxide	8013-07-8	(ESBO)				
Dipropylene glycol dibenzoate	27138-31-4			DGD		
Dioctyl sebacate	122-62-3		DOS			
Polyadipate	-	(Poly-adipate)				
DEHP			DEHP			

Hydrolysis

Many of the alternative plasticisers are, similarly to DEHP, esters of carboxylic acid compounds. Information on hydrolysis, which potentially may be an important environmental fate property for this type of substances, is rarely available and only very limited information has been found.

In general, hydrolysis of the carboxylic acid esters is rather slow except when the sidechain contains halogens or unsubstituted carbons. The process is also slower with the length of the alkyl chain. The dicarboxylic acid esters proposed as alternatives belong to groups of substances with relatively long alkyl chains. In Schwarzenbach et al. (1993) the estimated half time for hydrolysis of the relevant bond types range from 38 days to 140 years. In the same reference dimethyl phthalates are estimated to have hydrolysis half lives of 12 years at 10 °C and pH 7. A similar slow hydrolysis of the dialkyl acid ester bonds may be the case for DEHA, TETM, TXIB, DGD and DOS. For DEHA the BUA-review (BUA 1997) concludes on the prolonged reaction in a study performed at elevated pH and temperature, that hydrolysis under environmental conditions will proceed extremely slow.

Also for the tri-phosphate (BUA 1996) no significant hydrolysis is to be expected at typical environmental pH and temperature, which may also apply to DEHPA. An evaluation of the possible hydrolysis is not made for the remaining substances.

Migration

The substances display a range of migration potentials. The lipophilic substances such as DEHA, TETM, TXIB and DOS migrate to organic solvents and oil, whereas those with relatively high aqueous solubility migrate to water and weak acids (see Table 7.2).

Table 7.2
*Comparison of migration potential for assessed substances into fatty food simulant (**bold**) or water/acid. Tentative estimates for substances for which data is not available are given in parenthesis. DEHP is included for comparison.*

		Low		Medium			High
Name	CAS no.						
Diethylhexyl adipate	103-23-1			DEHA		**DEHA**	
O-acetyl tributyl citrate	77-90-7			ATBC	**ATBC**		
Di(2-ethylhexyl) phosphate	298-07-7		**DEHPA**				
Tri(2-ethylhexyl) phosphate	78-42-2	(TEHPA)		**(TEHPA)**			
Tri-2-ethylhexyl trimellitate	3319-31-1	TETM					**TETM**
O-toluene sulfonamide	88-19-7		**OTSA**			(OTSA)	
2,2,4-trimethyl 1,3-pentandioldiisobutyrate	6846-50-0		(TXIB)			**(TXIB)**	
Soybean oil epoxide	8013-07-8	**ESBO**					ESBO
Dipropylene glycol dibenzoate	27138-31-4		(DGD)			**(DGD)**	
Dioctyl sebacate	122-62-3	DOS					**DOS**
Polyadipate	-	(Polyester)	**(Polyester)**				
DEHP			DEHP		**DEHP**		

7.1.3 Humans

Four of the possible phthalate substitutes fulfil the criteria for classification with regard to acute toxicity or local effects. Based on the available literature DEHPA should be classified as Corrosive (C) and Harmful (Xn) with the risk phrases R34 (Causes burns) and R21 (Harmful in contact with skin). This classification was suggested by Bayer AG (Bayer, 1993) and is supported by the toxicological findings in the literature. TEHPA should be classified as Irritant (Xi) with the risk phrase R36/38 (Irritating to eyes and skin) also according to Bayer (1993). TETM fulfils the classification criteria with respect to acute toxicity as Harmful (Xn) with the risk phrase R20 (Harmful by inhalation) and DOS as Harmful (Xn) with the risk phrase R22 (Harmful if swallowed) based on LC_{50} and LD_{50} values. There are apparently no substances with severe organ effects, but the data set is very limited. It has not been possible to evaluate all effects according to their possible classification. The data are presented in Table 7.1.

The citrate, mellitate, epoxidised soybean oil, sebacate, and di-phosphate have been tested and found without CMR effects. One study showed foeto-

toxicity (reduced ossification) for DEHA in mice, but results were not statistically significant. The toluene sulfonamide may be the only of the substances having effects of the CMR type. However, the suspicion for OTSA is based on tests done in connection with assessments of saccharine and its impurities, among others OTSA. Here it was found that the impurities are responsible for the reproductive effects of impure saccharine. No results are available on the pure substance.

Only weak mutagenic activity was described and there is limited evidence that OTSA is carcinogenic when administered orally to rats. Based on the available data it cannot be assessed whether OTSA is responsible for these effects, although it is suggested in the studies.

The sensitisation effects have been tested for many of the substances and the adipate, citrate, di-phosphate, trimellitate, epoxidised soybean oil, and sebacate have been found not to have this effect. Only the PU precursor MDI is a recognised sensitiser.

It must be stressed that for the majority of the compounds an insufficient data set is available for a complete human health risk assessment.

7.1.4 Environment

The combination of high persistence and high bioaccumulation potential does warrant attention to uses that leads to emission to the environment. Such substances are possibly the mellitate, the citrate, the dibenzoate and the sebacate.

The compounds for which ecotoxicity data are available (only data for the aquatic environment available) show relativly high acute ecotoxicity, that in all cases would lead to an environmental hazard classification. For the trimellitate and the sebacate, the low aqueous solubility in combination with persistence and bioaccumulation potential would lead to a classification as 'May cause long term effects in the aquatic environment' (R53).

The polymer materials and the polyadipate are estimated as unlikely to give rise to effects in the aquatic environment.

No data was identified for the terrestrial environment.

7.2 Risk evaluation

It is beyond the scope of the present report to evaluate the risks associated with the use of the chemicals or materials in specific production, formulation or processing activities, since such evaluation must be coupled to a detailed knowledge of the particular technical and occupational environment. However, core properties such as volatility and migration are included. The data on risk is presented in Table 7.2.

7.2.1 Working environment

The exposure in the working has not been estimated at values above toxic values in the various scenarios, except for the adipate, where the selected scenario results in concentrations in workplace air 10^4 times the concentration resulting in more pronounced reactions in workers with an allergy or asthma case history.

In general, the loss of plasticiser will depend on the volatility of the compound. OECD has made an allocation of plasticisers into low, medium and

high classes of volatility (OECD 1998). Based in this the 11 plasticisers have been grouped relative to each other at standard 20-25 C.

7.2.2 Consumer exposure

Migration from PVC products has been measured for several of the alternative. In Table 7.2 it is attempted to show the migratory properties for the substances in a fatty food simulant (typically olive oil) and in an aqueous solvent (water or weak acids).

In the special teething ring scenario the citrate does reach 37% of a preliminary ADI of 1 mg/kg bw/day. The preliminary ADI is not officially recognised and a closer investigation of the citrate exposure conditions and human toxicity may be warranted.

7.2.3 Human exposure in environment/secondary poisoning

Several of the assessed substances have lipophilic properties based estimated $LogP_{ow}$ values, and they may consequently have a high tendency for accumulation in biota. This is particularly clear in the estimation of concentrations of the adipate and sebacate in root crops, and the ADI is exceeded for sebacate in the regional worst case scenario. Virtually all the daily dose of these substances to humans from the environment arises in the root crops. The EUSES model is not well calibrated at high $LogP_{ow}$ values and may overestimate the accumulation. However, some plants do accumulate anthropogenic substances and EUSES does not model this very precisely (Trapp, Schwartz, 2000). No data on terrestrial toxicity were identified to determine whether this accumulation may take place for these substances.

7.2.4 Aquatic ecosystems

The combination of high persistence and high bioaccumulation potential does warrant attention to uses that leads to emission to the environment. Such substances are possibly the mellitate, the citrate, the dibenzoate and the sebacate.

Toxicity in the environment (only data for aquatic organisms available) is also of concern. The adipate, the tri-phosphate and the epoxidised soybean oil display acute aquatic toxicities below 10 mg/l.

7.2.5 Sediment

The DEHA exceeds the risk quotient of one for the sediment compartment due to its sorptive properties, but only in the scenario with complete substitution to this substance. ATBC (limited data set), DEHPA, TEHPA, and TETM (limited data set) had risk quotients less than one. Several other substances could not be quantitatively assessed for risk in the sediment (or the aquatic) environment: TXIB, ESBO, OTSA, DGD, DOS. This applies to the materials as well.

7.2.6 Groundwater, soil and microorganisms

Only the toluene sulfonamide has a water solubility suggesting transport to groundwater. However, not only dissolved species are found in groundwater. Substances bound to dissolved organic matter are also found in the groundwater.

It must be stressed that a number of the assessed substances are lipophilic and may have a high affinity for sludge particles similar to that of DEHP. No data on terrestrial toxicity has been identified and very limited information on effects on microorganisms in the sewage treatment plant is found.

7.3 Overview

Assessment of chemicals is challenging when few and not necessarily the same parameters are available for all substances. A profound and comprehensive or quantitative ranking is by far a possibility with the data set presented for the substances and materials included in the present project. However, to allow for comparison among the substances and materials a compressed overview of the data and the (occasionally tentative) assessments is provided. It must be emphasised that the data sets rarely allow hazard and risk assessment strictly according to the various applicable guidelines, and that the assessment to some extent relies on data obtained in databases published by European and American authorities.

In the following two tables the properties of the alternatives to phthalates and to flexible PVC are considered. The choice of properties shown in Table 7.1 has been based on the hazard indicators for humans as mentioned in CSTEE (2000), i.e. carcinogenicity, reproductive and developmental effects, mutagenicity, sensitisation and severe organ toxicity supplemented here with assessment of acute and/or local effects. For the substances and materials evaluated none of three with sufficient data exhibited 'Severe organ toxicity' and this column has therefore been omitted (data was available for DEHA, ATBC and TETM). It should, however, be mentioned that one study from 1964 showed signs of CNS toxicity in rats and mice after intraperitoneal injection of 400 mg ATBC/kg bw. No supporting evidence for this effect has been found.

In addition to evaluating hazards, the risk is also assessed (Table 7.2). For humans this is achieved by comparing the estimated dose of the substance in consumer and environmental exposure with existing or estimated ADI. For the environment the environmental risk quotient is calculated from PNEC and estimated environmental concentrations.

Table 7.1
The inherent properties for the investigated subtances are summarised using key parameters: acute and local effects, carcinogenicity(C), genetic toxicity (M), reproductive toxicity (R), sensitisation, persistance, bioaccumulation and aquatic toxicity. If data are not available for all parameters or only from non standard test results a tentative assessment is given (shown in parentheses). For the materials an evaluation is given based on general polymer properties. The symbols: ● identified potential hazard, ○ no identified potential hazard, and – no data available.

		Humans			Environment		
Name of sub-stance	CAS No.	Acute and local effect (A/L)	CMR[d]	Sensitisa-tion	Persistence	Bioaccu-mulation	Aquatic Toxicity
Diethylhexyl adipate	103-23-1	○/○	(○)[a]	○	○	○	● very toxic
O-acetyl tributyl citrate	77-90-7	○/○	○ M, R	○	● (inherent)	(●)	● (harmful)
Di(2-ethylhexyl) phosphate	298-07-7	●/●	○	○	● (conflicting)	○	● harmful
Tri(2-ethylhexyl) phosphate	78-42-2	(○)/●	○ M, C	-	●	○	● harmful
Tri-2-ethylhexyl trimellitate	3319-31-1	●/○	○	○	●	(●)	-
O-toluene sulfonamide	88-19-7	-/-	(○)[c]	-	(●)	○	-
2,2,4-trimethyl 1,3-pentandiol diisobutyrate	6846-50-0	-/-	-	-	-	-	-
Epoxidised soy-bean oil	8013-07-8	-/○	○	○	○	-	● toxic
Dipropylene gly-col dibenzoate	27138-31-4	-/-	-	-	-[b]	(●)[b]	-[b]
Dioctyl sebacate	122-62-3	●/(○)	○	○	-	(●)	-
Polyadipates	-	-/-	-	-	- (persistent)	- (unlikely)	- (unlikely)
PU (MDI)	101-68-8	●/●	(○)	●	- (persistent)	- (unlikely)	- (unlikely)
LDPE	9002-88-4	-/-	-	-	- (persistent)	- (unlikely)	- (unlikely)

[a] Foetotoxicity (reduced ossification) has been identified as the most sensitive effect in a developmental toxicity study.
[b] QSAR estimates by Danish EPA leads to the classification N; R50/53 (May cause long term effects in the aquatic environment).
[c] A test on reproductive effects performed on a product containing OTSA as impurity attributes effect to OTSA. No substance specific data available.
[d]C,M,R indicated that the effect is investigated but no effects are seen.

Table 7.2
The evaluated risks to humans or the environment are summarised for the investigated substances (the polymer materials are not included). The estimated exposure of humans is compared to the Acceptable Daily Intake (ADI). Predicted environmental concentrations in the aquatic environment (PEC) are compared to predicted no-effect concentrations (PNEC). "Worst case" scenarios are used. The reader is referred to the main text and the data sheets for further explanations to the table. Parentheses show an assigned ADI. The symbols: ● ratio >1 (identified potential risk), ○ ratio <1 (no identified potential risk), and –no data available.

Substance or material	CAS no.	Ratio of dose to ADI		Ratio of PEC to PNEC		Remarks (ADI in mg/kgbw/d)
		Consumer	Humans from environment	Water	Sediment	
Diethylhexyl adipate	103-23-1	○	○	○	●	ADI 0.3
O-acetyl tributyl citrate	77-90-7	(○)[a]	(○)	○[b]	○[b]	Preliminary ADI 1.0[c]
Di(2-ethylhexyl) phosphate	298-07-7	○	○	○	○	Group ADI 0.05
Tri(2-ethylhexyl) phosphate	78-42-2	○	○	○	○	Group ADI 0.05
Tri-2-ethylhexyl trimellitate	3319-31-1	(○)	○	○[d]	○[d]	Assigned ADI 0.05
O-toluene sulfonic acid amide	88-19-7	(○)	(○)	-	-	Assigned ADI 0.05
2,2,4-trimethyl 1,3-pentandiol diisobutyrate	6846-50-0	-	-	-	-	No exposure data
Epoxidised soybean oil	8013-07-8	-	-	-	-	No exposure data
Dipropylene glycol dibenzoate	27138-31-4	(○)	(○)	-	-	Assigned ADI 0.05
Dioctyl sebacate	122-62-3	○	●	-	-	Group ADI 0.05

[a] Dose reaches 37% of preliminary ADI in teething ring scenario.
[b] Tentative estimate based on only one ecotoxicity study.
[c] Preliminary ADI from Nikiforov (1999)
[d] Data set comprise only two acute values and one chronic NOEC value.

8 Conclusions

Physical chemical parameters

Key parameters with respect to release of plasticisers under polymer production and consumer use are their potential for evaporation and migration out of the PVC polymer. Some data exists for volatility, but only few data has been identified on migration potential for the substitutes.

Hazardous properties

Available toxicity data for acute and local effect suggests classification for some of the substances. This is the case for di(2-ethylhexyl) phosphate which should be 'Corrosive' (R34) and 'Harmful' (R21), tri(2-ethylhexyl)phosphate which should be 'Irritant' (R36/38), tri-2-ethylhexyl trimellitate which should be 'Harmful' (R20) and dioctyl sebacate which should be 'Harmful' (R22). The classification for the phosphates is suggested by Bayer AG and supported by the literature. For other effects it is either not possible to suggest a classification based on the reviewed literature or the substances do not display these effects.

The substances for which data are available for some of the critical properties toward humans, such as CMR, sensitisation etc., do not display such effects based on the available data. This concerns diethylhexyl adipate, o-acetyl tributyl citrate, tri-2-ethylhexyl trimellitate, epoxidised soybean oil and the dioctyl sebacate. For some substances the available data suggest that reproductive and developmental toxicitity is investigated further in order to conlude about a possible effect. This is the situation for diethylhexyl adipate, o-acetyl tributyl citrate, tri(2-ethylhexyl)phosphate, o-toluene sulfonamide and epoxidised soybean oil.

The compounds for which ecotoxicity data are available (only data for the aquatic environment available) show relatively high acute ecotoxicity that in all cases would lead to an environmental hazard classification. The adipate would be 'Very toxic' (R50/53) and epoxidised soybean oil is classifiable as 'Toxic' (R51/53). O-acetyl tributyl citrate, di(2-ethylhexyl) phosphate and tri(2-ethylhexyl) phosphate would be classified as 'Harmful' (R52/53). For the trimellitate and the sebacate, the low aqueous solubility in combination with persistence and bioaccumulation potential would lead to a classification as 'May cause long term effects in the aquatic environment' (R53).

It is emphasised that for o-toluene sulfonamide, diisobutyrate (TXIB), epoxidised soybean oil, dipropylene glycol dibenzoate and dioctyl sebacate the lack of data regarding ecotoxicity is limiting the assessment. The tentative classification of the citrate and trimellitate is based on only one and two studies, respectively (the citrate study is almost 30 years old).

Degradability

Several substances show limited degradability in the environment (the trimellitate and possibly both phosphates). Some have a high estimated bioaccumulation potential (citrate, trimellitate, dibenzoate and sebacate). The trimellitate possibly combines both of the environmentally undesired properties. It must be emphasised that this is based on estimated values for bioaccumulation based on estimated octanol-water partition coefficients. It is possible that these compounds to some extent degrades through hydrolysis in the environment and the bioaccumulation is then expected to be considerably less. Although no data on the dibenzoate and sebacate are available similar processes may apply to these structurally related compounds. Meas-

ured bioaccumulation for the adipate and the two phosphates are below the criteria for bioaccumulation.

Risk for humans from environment

A possible risk to humans has only been suggested by the selected scenarios for a few of the substances and primarily in relation to the workplace scenarios. The workplace scenario considers aerosol generation in connection with production of floor and wall coverings using a process temperature of 200°C and eight exposure events per day, which is most likely a very conservative scenario. For the adipate the selected scenario results in concentrations in workplace air 10^4 times the concentration resulting in more pronounced reactions in workers with an allergy or asthma case history. For the two phosphates the estimated concentrations were lower than observed effect levels in animal studies, but within commonly used safety margins.

The estimated exposure of consumers and the public to the phthalate alternatives were generally much lower than the established ADI value even in the worst case scenarios. Only the worst case scenario for dioctyl sebacate displayed doses exceeding the ADI (conservatively) based on peroxisome proliferation data for di-ethylhexyl phthalate. The human exposure comes almost exclusively from the contribution by root crops due to high estimated octanol-water partitioning values and the low biodegradation potential. Only limited toxicological and ecotoxicological data are available and conservative default values are used. More data may very well change the risk perception.

The citrate does reach 37% of a preliminary ADI of 1 mg/kg bw/day in a teething ring scenario. The preliminary ADI is not officially recognised and a closer investigation of the citrate exposure conditions and human toxicity may be warranted.

Risk for the environment

The risk quotient does not exceed one (the critical value) in the water phase for any of the five compounds for which it could be calculated (diethylhexyl adipate, o-acetyl tributyl citrate, di(2-ethylhexyl) phosphate, tri(2-ethylhexyl) phosphate, and tri-2-ethylhexyl trimellitate). The adipate exceeded the risk quotient of one for the sediment compartment due to the lipophilicity. PEC/PNECs could not be calculated for o-toluene sulfonamide, the diisobutyrate (TXIB), epoxidised soybean oil, dipropylene glycol dibenzoate and dioctyl sebacate.

Terrestrial and microbial toxicity

It must be stressed that a number of the assessed substances are lipophilic and may have a high affinity for sludge particles similar to that of DEHP. No data on terrestrial toxicity has been identified and very limited information on effects on microorganisms in the sewage treatment plant was found (effects were typically not in the tested range of concentrations).

Assessment of polymer materials

Due to the assessment principles of the EU TGD the materials and the polyadipate plasticiser are assessed by expert judgement. The polymer materials and the polyadipate are estimated as unlikely to give rise to effects in the aquatic environment. In general, no effects are expected in the consumer use situation of these.

Data availability

The data availability varies among the suggested alternatives for phthalate plasticisers and materials. For di(2-ethylhexyl) adipate, o-acetyl tributyl citrate, tri(2-ethylhexyl) phosphate and tri-2-ethylhexyl trimellitate information is available covering a range of results from tests on toxicological properties. However, only di(2-ethylhexyl) adipate can be considered adequately

covered, although some areas need further investigation. Di(2-ethylhexyl) phosphate, o-toluene sulfonamide, 2,2,4-trimethyl 1,3-pentandiol diisobutyrate, epoxidised soybean oil, dipropylene glycol dibenzoate and dioctyl sebacate are covered in less detail, either because of lack of information or because of inferiour quality of the tests.

For di(2-ethylhexyl)adipate a large number of studies are covering acute toxicity, local effects, sensitisation, repeated dose/chronic toxicity, genetic toxicity, reproductive toxicity and carcinogenicity. Reviews discussing the toxicological profile of the substance are also available. In a substitution context it is however important to consider all areas which may give rise to concern, to make sure that only less hazardous substituents are introduced. Based on comparisons with the structural analogue, di(2-ethylhexyl) phthalate, for which the most critical effect is considered to be testicular toxicity, a need to address this issue for the adipate as well has been identified.

For o-acetyl tributyl citrate the available data are not sufficient for a profound assessment. Data on acute toxicity are sparse and other effects like carcinogenicity are not sufficiently covered for a qualified assessment.

For the two phosphates, di(2-ethylhexyl)phosphate and tri(2-ethylhexyl)phosphat, a number of studies are available, sufficient to suggest a classification of the substances for acute and local effects. Studies on repeated dose and chronic toxicity like reproductive toxicity and carcinogenicity are either not available or not sufficient for an assessment.

For tri-2-ethylhexyl trimellitate a number of studies are available covering acute and local effects. More details are however needed in order to classify the substance with regard to irritant effects. More data are also needed on repeated dose and chronic toxicity studies. Reproductive toxicity is not covered at all in the reviewed literature.

O-toluene sulfonamide is sparsely covered in the literature and no data are found available on acute toxicity. Few studies are available on other effects, but not sufficient for a qualified assessment or classification. Human data are only available for related substances or combined products.

Few data are available for 2,2,4-trimethyl 1,3-pentandiol diisobutyrate. In order to make a proper evaluation of acute toxicity more detailed information is necessary. Repeated dose and chronic toxicity are not covered in the reviewed information.

A limited number of studies are available for epoxidised soybean oil. Studies on acute toxicity suggest low toxicity, but more detailed information is needed for a proper evaluation. Data on repeated dose toxicity and chronic effects are also insufficient for a qualified assessment.

No toxicological data have been found for dipropylene glycol benzoate.

Also dioctyl sebacate is sparsely covered in the available literature. Few data are available describing acute toxicity and only oral toxicity has been evaulated. Data on other effects are not sufficient for an evaluation.

No toxicological data have been found for polyester (polyadipate).

Regarding environmental properties only di(2-ethylhexyl) adipate, o-acetyl tributyl citrate, and tri(2-ethylhexyl) phosphate have a data set comprising

algae, crustaceans and fish, and data on biodegradation. The remaining substances have very few or no ecotoxicological data. There are very few data on chronic endpoints, very limited data on effects on microorganisms and no data on terrestrial ecotoxicity.

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Appendices

Appendix 1:
Abbreviations used

Abbreviations used

Abbreviation	Explanation
ADI	Acceptable daily intake
ATBC	O-acetyl tributyl citrate
BCF	Bioconcentration factor
BOD	Biological Oxygen Demand
bw	Body weight
d	day
DEHA	Di(ethylhexyl) adipate
DEHP	Di(2-ethylhexyl) phthalate
DEHPA	Di(2-ethylhexyl) phosphate
DGD	Dipropylene glycol dibenzoate
DIN	Deutsche Industrielle Norm
DINP	Diisononyl phthalate
DOS	Dioctyl sebacate
Dw	Drinking water
EASE	Estimation and Assessment of Substance Exposure
EC_{50}	Effect concentration for half population
ECB	European Chemicals Bureau
EPA	(US) Environmental Protection Agency
ESBO	Epoxidised soy bean oil
EU	European Union
EUSES	European Uniform System for the Evaluation of Substances
fw	Fresh water
h or hrs	hour or hours
HPVC	High Production Volume Chemical
i.p.	intra peritoneal (in blood stream)
i.v.	intra venous (in a vein)
IARC	International Agency for Research on Cancer
IUCLID	International Uniform Chemical Information Database
LC_{50}	Lethal concentration for half population
LD_{50}	Lethal dose for half population
LDPE	Low Density Polyethylene
LOAEL	Lowest observed adverse effect level

Abbreviations used

Abbreviation	Explanation
$LogP_{ow}$	Octanol water partitioning coefficient
Lw	Lake water
MDI	Methylene phenylene diisocyante
NOAEL	No observed adverse effect level
NOEC	No observed effect concentration
OECD	Organisation for Economic Coorperation and Development
OTSA	O-toluene sulfonamide
PEC	Predicted Environmental Concentration
PNEC	Predicted No-Effect Concentration
ppm	Parts per million (e.g. mg/l)
PU	Polyurethane
PVC	Polyvinyl chloride
Rw	River water
sw	Salt water
S_w	water solubility
TDI	Tolerable Daily Intake
TEHPA	Tri(2-ethylhexyl) phosphate
TETM	Tri-2-ethylhexyl trimellitate
TGD	Technical Guidance Document
TXIB	2,2,4-trimethyl 1,3-pentanediol diisobutyrate
UDS	Unscheduled DNA synthesis
w/w	Weight/weight
ww	Wet weight

SI units are not included in list of abbreviations.

Appendix 2:

Standard conditions for exposure scenario

Appendix 2 Table 1

EUSES scenario overview

Substance	Substitution type	Amount substituted (tons)
Di(ethylhexyl) adipate	Complete	10735
	Partial	1703
O-acetyl tributyl citrate	Complete	10735
	Partial	554
Di(2-ethylhexyl) phosphate	Complete	10735
	Partial	2040
Tri(2-ethylhexyl) phosphate	Complete	10735
	Partial	2244.5
Tri-2-ethylhexyltrimellitate	Complete	10735
	Partial	1853.4
Alkylsulfonic acid ester	Complete	10735
	Partial	30
Dipropylene glycol dibenzoate	Complete	10735
	Partial	204
Dioctyl sebacate	Complete	10735
	Partial	110

Appendix 2 Table 2
EASE scenario overview

Substance	Scenario type	Scenario description
Di(ethylhexyl) adipate	Worker	Production of floor and wall covering
	Consumer	Daily use of a bathroom with floor and wall coverings
O-acetyl tributyl citrate	Worker	Production of printing inks
	Consumer	Daily reading of printed advertisement and Daily use of PVC-toys
Di(2-ethylhexyl) phosphate	Worker	Production of cables – open tube after the extruders
	Consumer	Exposure from cables in private houses
Tri(2-ethylhexyl) phosphate	Worker	Production of cables – open tube after the extruders
	Consumer	Exposure from cables in private houses
2,2,4-trimethyl 1,3-pentandiol diisobutyrate	Worker	Production of cables – open tube after the extruders
	Consumer	Exposure from cables in private houses
Alkylsulfonic acid ester	Worker	Production of cables - open tube after the extruders
	Consumer	Exposure from cables in private houses
Dipropylene glycol dibenzoate	Worker	Production of fillers
	Consumer	Daily use of a bathroom with fillers
Dioctyl sebacate	Worker	Production of printing inks
	Consumer	Daily reading of printed advertisement

Appendix 3:

Organisations Contacted

Authorities

The Danish Environmental Protection Agency, Copenhagen, Denmark

Swedish National Chemicals Inspectorate, Stockholm, Sweden

National Working Environment Authority, Copenhagen, Denmark

The Medicines Agency, Copenhagen, Denmark

The Danish Veterinary and Food Administration, Copenhagen, Denmark

Occupational Health Inspectorate, Copenhagen, Denmark

National Environmental Research Institute, Copenhagen, Denmark

Trade organisations

The Danish Plastics Federation, Denmark

Members of the Danish Paintmakers Association

European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Brussels, Belgium

The Graphic Association of Denmark (GA)

PVC Information Council Denmark

Federation of Danish Textile and Clothing (FDTC)

European Counsel for Plasticisers and Intermediates, Brussels, Belgium

Association of Plasticisers Manufacturers in Europe, Brussels, Belgium

Industries

AEC Rådgivende Ingeniører, Vedbæk, Denmark

AKV Gummi, Laasby, Denmark

Akzo Nobel Chemicals, Skovlunde, Denmark

Aalborg Gummivarefabrik, Aalborg, Denmark

Alifix, Kolding, Denmark

A-Trading Fugekemi, Nr. Sundby, Denmark

BASF Danmark, Copenhagen, Denmark

Bayer DK, Lyngby, Denmark

Berner, Nørresundby, Denmark

Bjørn Thorsen Polymer, Copenhagen, Denmark

CASCO, Fredensborg, Denmark

Ciba Special Chemicals, Virum, Denmark

Clariant, Glostrup, Denmark

CODA GUMMI, Køge, Denmark

DAFA, Brabrand, Denmark

DANA LIM, Køge, Denmark

DAN-KIT, Græsted, Denmark

DOW, Stockholm, Sweden

DOW CORNING, Stockholm, Sweden

DOW CORNING, United Kingdom

DTI, Taastrup, Denmark

EniChem, Copenhagen, Denmark

Exxon Chemicals, Göteborg, Sweden

Exxon Chemicals, Copenhagen, Denmark

Hempel, Lyngby, Denmark

Henkel Byggeteknik, Vejle, Denmark

ICI Norden, Göteborg, Denmark

KEMOPLAST, Hvidovre, Denmark

Kondor Kemi, Glostrup, Denmark

LIP, Nr. Åby, Denmark

Mont Oil, Stockholm, Sweden

Neste Oxo AB, Stenungsund, Sweden

NKT Cables, Kalundborg, DK

Nordisk Byggekemi, Rødekro, Denmark

Norsk Hydro, Copenhagen, Denmark

Optirock, Karlslunde, Denmark

PCI Augsburg, Germany

Reilly Chemical, Brussels, Belgium

Rodia (tidligere Rhône Poulenc), Søborg, Denmark

Sika-Beton, Lynge, Denmark

Sika, Zürich, Switzerland

Sveda Kemi, Frederiksberg, Denmark

TOTALFINA, Paris, France

W.R. Grace & Co, Maryland, US

Åffa, Ishøj, Denmark

Appendix 4:

Physical-chemical, emission, exposure, health and environmental data

The complete result of the screening for environmental and health data is given in the data sheets presented in the appendix. Each data collection has been based primarily on review literature, handbooks and electronic data-bases and for selected key studies on the original paper, if available. The first page of each data sheet presents a short summary of the most important findings and if relevant a remark regarding special properties of the com-pound.

The information marked by ♦ in the data sheets of appendix 4 is considered key data for the assessment.

The list of literature represents the sources of information, which have been consulted. Not necessarily all references are quoted in each table.

Diethylhexyl adipate

CAS number: 103-23-1

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

The reviewed data on diethylhexyl adipate (DEHA) indicates that the substance is non-volatile and slightly flammable compound with low water solubility. Further, the available data on $LogP_{ow}$ indicates strong lipophilicity and partitioning to particles and biota. DEHA has a migration potential in PVC films, which in several cases exceeds the Danish limit of 4 mg/dm^2.

Emission

DEHA is according to the available estimates released during production, and from consumer products.

Exposure

DEHA has been found in the aquatic environment, in drinking water and in sewage sludge. DEHA has also been found to migrate into food, which has been in contact with cling films.
Occupational exposures occur during the production.

Health

The lowest LD_{50} was 7,392 mg/kg bw in rat in acute oral tests. Acute effects were not observed from DEHA in inhalation studies nor was DEHA shown to be sensitising. DEHA was slightly irritating to skin and eyes in rabbits.
The subacute NOAEL was 610 mg/kg bw in rat and more than 3,100 ppm in mouse.
DEHA was only slightly mutagenic in *in vitro* tests. Studies on dominant lethal mutations in mouse showed a LOAEL on 450 mg/kg bw. Metabolites showed no mutagenic effects in Ames tests with *Salmonella typhimurium*.
DEHA shows limited evidence of carcinogenicity in animals (IARC, category 3).
NOAEL was 170 mg/kg bw/day for both the parent and the F_0 generation in reproductive toxicity studies in rats. The NOAEL was 170 mg/kg/day and LOAEL was 1,080 mg/kg/day to rat in reproductive toxicity tests.
Critical effect: NOAEL, foetotoxicity was 28 mg/kg bw/d.
Several hexyl carboxylic acid derivated metabolites have been identified in humans. Elimination half-life of DEHA was only 1½ hour. Distribution of DEHA was highest in body fat, liver and kidney when adminis-

tered once intravenous or intragastrically to mouse and rat. No DEHA was observed in mouse after 4 days.

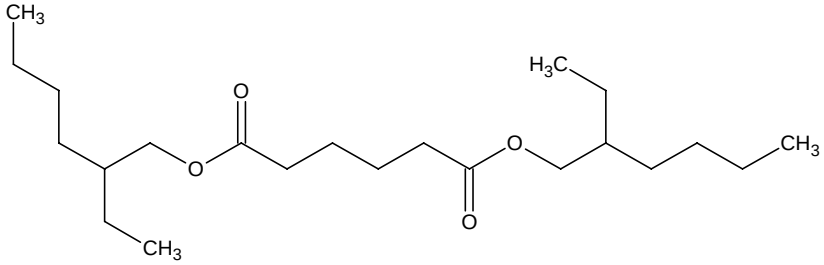
Based on the available data, DEHA does not fulfil the criteria for classification according to the Substance Directive /EU 1967/ for any of the described effects.

Environment

According to the available biodegradation data there is good evidence of ready biodegradability of DEHA. In one study DEHA is very toxic to *D. magna* with 50% mortality slightly below 1 mg/l. The available ecotoxicological data on DEHA from several other experiments show no mortality in algae, crustaceans, and three fish species at concentrations up to 100 times the water solubility of DEHA. The maximum acceptable toxicant concentration in a chronic test on reproduction in *D. magna* was 0.024-0.052 mg/l. Bioaccumulation was 27 in test with bluegills, 100 times less than predicted from $LogP_{ow}$.

Diethylhexyl adipate

Identification of the substance

CAS No.	103-23-1
EINECS No.	203-090-1
EINECS Name	Bis(2-ethylhexyl) adipate
Synonyms	Adipic acid bis(2-ehtylhexyl) ester, adipol 2 EH, AI3-28579, BEHA, bis(2-ehtylhexyl) adipate, bis(2-ethylhexyl)ester adipic acid, bis(2-ethylhexyl)ester hexandioic acid, bis(2-ehtylhexyl) hexanedioate, bisoflex DOA, D, DEHA, di-2-ethylhexyl adipate, di(2-ethylhexyl) adipate, diethylhexyl adipate, di-octyl-adipat, diisooctyladipat, dioctyl adaipate, DOA, Effemoll DOA, Effomoll DA , Effomoll DOA, ergoplast ADDO, flexol A 26, flexol plasticiser 10-A, Flexol plasticiser A-26, Flexol plasticiser A 26, hexanedioic acid, bis(2-ehtylhexyl) ester, exanedioic acid, bis(2-ehtylhexyl) ester (9CI), hexanedioic acid, di(2-ehtylhexyl) ester, hexanedioic acid, dioctyl ester, Kemester 5652, Kodaflex DOA, Lankroflex DOA, Mollan S, Monoplex, Monoplex DOA, NCI-C54386, NSC 56775, octyl adipate, Plastomoll, Plastomoll DOA, PX-238, Reomol DOA, Ruco-flex plasticiser DOA, Sicol, Sicol 250, Staflex DOA, Truflex DOA, Uniflex DOA, Vestinol OA, Wickenol 158, Witamol, Witamol 320.
Molecular Formula	$C_{22}H_{42}O_4$
Structural Formula	

Major Uses	Plasticiser in PVC and other polymers processing.	[3]
	Hydraulic fluid.	[3]
	Plasticiser or solvent in cosmetics.	[3]
	Plasticiser in PVC films.	[3]
	Aircraft lubrication.	[12]
	Application of paints and coatings.	[12]
IUCLID	The compound is included on the IUCLID HPVC list.	
EU classification	The compound is not included in Annex I to 67/548/EEC	

Diethylhexyl adipate

Physico-chemical Characteristics

Physical Form	Colourless or very pale amber liquid. Light-coloured, oily liquid. Clear colourless liquid. Colourless liquid	[3] [6] [6] [15]
Molecular Weight (g/mole)	370.57	
Melting Point/range (°C)	♦-67.8 –65 to –79 –65 –76 (DIN-ISO 3016)	[13] [1,10,12] [15] [16]
Boiling Point/range (°C)	210-218 ♦417 214 (at 5 mm Hg) 210-218 (DIN 53171, at 20.7 mm Hg) 210-220 (at 14.8 mm Hg) 210-218 (at 5.5 mm Hg, DIN 53171)	[1] [13] [3,12] [10] [15] [16]
Decomposition Temperature (°C)	No data found	
Vapour Pressure (mm Hg at °C)	1.58 (100 °C) 2.4 (200 °C) 8.5×10^{-7} (20 °C) <0.01 (20 °C) 2.35×10^{-6} (calculated, 25°C) ♦8.50×10^{-5} (20 °C) 2.6 (20 °C) 0.03 (20 °C) 0.016 (100 °C)	[1] [2] [3] [8] [8] [10] [12] [15] [16]
Density (g/cm^3 at °C)	0.924 (DIN 51757, 20 °C) 0.922 (25 °C) 0,9268 (20 °C) 0.923-0.926 (20 °C)	[1,10,16] [3] [6] [15]
Vapour Density (air=1)	12.8	[3]
Henry's Law constant ($atm/m^3/mol$ at °C)	4.34×10^{-7} (measured, 20 °C) 4.34×10^{-7} (measured, 25 °C) 2.13×10^{-5} (estimated, 25°C)	[3] [10] [8]
Solubility (g/l water at °C)	<0.1 (20 °C) <0.1 (22 °C) ♦0.00078 (22 °C) 0.1 (estimated, 25 °C) 0.2 (20 °C)	[1,16] [6] [3,6] [10] [10]

Diethylhexyl adipate

Partition Coefficient (log P_{ow})	♦8.114 (estimated) ♦> 6.11 (measured) 4.2 (estimated) ♦8.1-8.114 (estimated) 6.114-8.2 (estimated) ♦8.1 (estimated)	[1] [3] [8] [10] [10] [12,15]
pK_a	Not applicable	
Flammability	Slightly flammable when exposed to heat ♦Must be preheated before ignition	[3] [6]
Explosivity	No data found	
Oxidising Properties	No data found	
Migration potential in polymer	From PVC films to isooctane: 8.1-48.1 mg/dm^2 From PVC to olive oil: 8.2-41.3 mg/dm^2 (reduced 2.6-41.3 mg/dm^2)	 [14] [14]

Emission Data

During production	Estimated: ♦Ca. 1 % to atmosphere of treated amount of plastizicer 0.001 % to hydrosphere of total production amount	 [10] [10]

Exposure Data

Aquatic environment, incl. sediment	Measured: Rw winter 0.08-0.3 ppb Rw 1-30 ppb Lw 35-130 ng/l Fw 0.2-1.0 µg/l Lw 0.01 –7.0 µg/l Untreated dw 0.02 µg/l Rw 1 µg/l Indust. effluent 8.2 µg/l Sediment 0.1 mg/kg Lake sediment 3 mg/kg dry weight	 [3,12] [3] [3,10] [3] [10] [10] [10] [10] [10] [10]
Terrestrial environment	No data found	

Diethylhexyl adipate

Sewage treatment plant	Measured:	
	Effluent 2-70 ppb	[3]
	Effluent 2000 ppb	[3]
	Effluent 10 µg/l	[10]
	Influent 90 µg/l	[10]
	Influent 0.1-3 µg/l	[10]
Working environment	Measured:	
	Indoor, office 2 ng/m^3	[3]
	Indoor, packing room max 214 µg/m^3	[10]
	Indoor, laboratory 0.001-0.0014 µg/m^3	[10]
	Indoor, telephone exchange 0.002 µg/m^3	[10]
	Indoor, meat packing room av. 11.7 µg/m^3	[10]
	Indoor, meat packing room max 14.7 µg/m^3	[10]
Consumer goods	No data found	
Man exposed from environment	No data found	
”Secondary poisoning”	Measured:	
	Dw 77 ppb	[3]
	Dw 0.002 ppb	[3,10]
	Dw 0.1 µg/l	[3]
	Dw 20.0 µg/l	[3]
	Fruits/vegetables 0.2-6.4 mg/kg	[3]
	Sandwich 30-325 mg/kg	[3,10]
	Cheese 28-2,100 mg/kg	[3]
	Fresh pork 1.8-64 mg/kg	[3]
	Fresh lamb 2.9-11 mg/kg	[3]
	Fresh beef 1.0-8.0 mg/kg	[3]
	Fresh chicken 8.5-53 mg/kg	[3]
	Draught beer 0.01-0.07 mg/kg	[3]
	Bottled beverage 0.01-0.1 mg/kg	[3]
	PVC wrapped food 41-362 mg/kg	[3]
	Mango slices 0.2 mg/kg	[10]
	Cabbage 4.8 mg/kg	[10]
	Cake slices 200 mg/kg	[10]
	55 % Minced beef 81.8 mg/kg	[10]
	Olive oil 192-391 mg/kg	[10]
	Chocolate 0.38 mg/kg	[10]
	Biscuits 0.11 mg/kg	[10]
	Cheese 15-2100 mg/kg	[10]
	Fresh meat 49-151 mg/kg	[10]
	Boiled meat 40 mg/kg	[10]
	Dialysis patients (1-5h) 2.7-9.7 mg/l perfusate	[10]
	Oxplasma (5h) 80-90 mg/l	[10]
	Human plasma 50-100 mg/l blood	[10]
		[10]

Diethylhexyl adipate

Atmosphere	Measured: Coal smoke 73 μg/Nm^3	[10]
	Estimated: Rain 1 μg/l Air 15–20 pg/m^3	[10] [10]
Dermal	No data found	

Toxicological data

Observations in humans	Irritation and sensitisation: The concentration of DEHA in working environment was at 4 workplaces below detection limit. Only one worker reported having difficulties with the respiratory passages.	[1,10]
	♦In the meatpacking industry 685 workers were investigated. The average DEHA concentration in the rooms was 11.7 μg/m^3 to 14.6 μg/m^3. Workers with asthma or allergy seemed to have more pronounced reactions.	[1]
	0.01-0.225% (4 testrows) 370 persons. One incidence of mild skin reaction.	[10]
	0.175% to 9% DEHA in cosmetic products151 subjects mild skin irritation was observed in two subjects in induction tests with. (CFTA 1976).	[29]
	Cosmetic products containing 0.175% to 9% of DEHA. Mild irritation was observed in two of 151 human subjects at the induction tests. Repeated insult patch test.	[10]
	9% DEHA in cosmetic product (3 times per w for 3 w) 209 subjects. Light to strong erythema was observed in 4 of 209 subjects (BIBRA/CFTA 1978A).	[10,31]
	Undiluted DEHA. Not sensibility observed.	[10]
	9% (repeated treatment) 25 subjects. No photo-sensibilisating reactions observed.	[10]
	ADI: ♦ADI for man : 0.3 mg DEHA/kg bw/d	[23]
	Toxicokinetics 50 mg H2 marked DEHA in 6 test persons. 2-ethyl-5-hydroxyhexanoic acid was observed as the main metabolite in the urine.	[1,10]

	♦46 mg/person (once) administration in an oral gelantine capsule. Metabolites in blood (up to 31 h after administration) and urine (up to 96 h after administration) investigated. The main metabolite in blood was 2-ethylhexyl acid. Elimination half time was 1.65 h. In urine the observed metabolites were 2-ethylhexylanoic acid (8.6%), 2-ethyl-5-hydroxyhexanoic acid (2.6%) 2-ethyl-1,6-hexandioicacid (0.7%), 2-ethyl-5-ketohexanoic acid (0.2%) and 2-ethylhexanol (0.1%). Half life time was approx. 1.5 h. After 36 h no metabolites were found in the urine.	[10,40]
	50 mg (single) oral administration. Metabolites after 24 h in humans investigated in urine and faeces. 1.5-8 % 2-ethyl-5-hydroxyhexanacid, 0.5-1.5% 2-ethyl-5-ketohexanacid. 0.15-1% 2-ethyl-1,6-hexandiacid. In faeces di-(2-ethylhexyl)adipate and mono-(2-ethylhexyl)adipate were found.	[10,41]

Acute toxicity

Oral	Rat:	
	Test dose not given. LD_{50} was 45,000 mg/kg bw.	[1,10]
	Test dose not given. LD_{50} was 24,600 mg/kg bw.	[1,10]
	Test dose not given. LD_{50} was 14,800 mg/kg bw.	[1,10]
	♦Test dose not given. LD_{50} was 7,392 mg/kg bw.	[1,10, 24]
	Test dose not given. LD_{50} was 9,110 mg/kg bw.	[1,10]
	Test dose not given. LD_{50} was 20,290 mg/kg bw.	[1,10]
	Test dose not given. LD_{50} was 20,000-50,000 mg/kg bw.	[1,10]
	Test dose not given. LD_{50} was 9,110 mg/kg	[6,10]
	Test dose not given. LD_0 was 6,000 mg/kg	[10]
	Mouse:	
	Test dose not given. LD_{50} was 15,000 mg/kg bw.	[1,10]
	Test dose not given. LD_{50} was 24,600 mg/kg bw.	[1,10]
	Guinea pig:	
	Dose≤14 ml/kg. Effects: 50% died after 2-3 d	[3]
	Test dose not given. LD_{50} was 12,900 mg/kg bw.	[1,10]
Dermal	♦Test dose not given. LD_{50} was 8,410 mg/kg	[1,6,10,26]
	Test dose not given. LD_{50} was 15,100 mg/kg	[1]
Inhalation	Rat:	
	8h exposure, no effects observed	[1]
	♦900 g/m^3 (4 hours). No effects	[27]

Other routes	Rat: i.v., LD_{50}=900 mg/kg bw	[1,6,10]
	Rabbit: ♦i.v., LD_{50}=540 mg/kg bw	[1,6,10,28]
	Rat: Test dose not given. i.p., LD_{50}>6,000 mg/kg bw Test dose not given. i.p., LD_{50}>46,000 mg/kg bw Test dose not given. i.p., LD_{50}>47,000 mg/kg bw	[1,10] [1] [1]
	Mouse: ♦Test dose not given. i.p., LD_{50} ca. 150 mg/kg bw Test dose not given. i.p., LD_{50}>5,000, mg/kg bw, GLP Test dose not given. i.p., LD_{50}>5,000 mg/kg bw Test dose not given. i.p., LD_{50}>9,240 mg/kg bw Test dose not given. i.p., LD_{50}>92,400 mg/kg bw Test dose not given. i.p., LD_{50} app. 150,000 mg/kg bw	[1,25] [1] [1] [1] [1] [1]
	Rabbit: Test dose not given. i.p., LD_{50}>38,000 mg/kg bw	[1,10]
Skin irritation	Rabbit: Test dose not given. Not irritating (5 studies) ♦500 mg; Test dose not given. Slightly irritating (2 studies)	[1,10] [1,10,26]
Eye irritation	Rabbit: No dose specified. Not irritating, BASF test. 0.1 ml (92.4 mg). Not irritating. No dose specified. Not irritating, Draize test. ♦0.5 ml (462 mg) test substance. Small foci with necroticism. 500 mg. Slightly irritating. Test dose not given (24 h) particular attention to cornea. Degree of injury rated 1. Most severe injury has been rated 10. No dose specified. Temporary redness of conjunctive. No effects observed after 24 hours.	[1] [1,10] [1] [1,10,20] [1,10] [3, 19] [10]
Irritation of respiratory tract	No data found	
Skin sensitisation	Guinea pig: Application of o.05ml/0.1% and weekly o.1ml/0.1% over (3 w). Not sensitising, Draize test	[1,10]
	♦First application 0.05 ml 0.1% solution, thereafter 0.1 ml 0.1 % solution 3 times/w (3 w) 10 males. Not sensitising, patch test.	[1,10,30]

Diethylhexyl adipate

Subchronic and Chronic Toxicity

Oral	Many other studies found.	
	Mouse:	
	700 and 1,500 mg/kg/d (2-year) feeding. Dose related depression of weight gain.	[4]
	♦ *B6C3F1* mice: 240-3,750 mg/kg bw (13 w) feeding. Decrease in weight gain in male mice at 465 mg/kg bw.	[1,10,21]
	♦ *B6C3F1* mice: 32-3,322 mg/kg bw (21 d) feeding. Decrease in weight gain, increased liver weight and peroxisome numbers in liver cells above 325 mg/kg bw. NOAEL=325 mg/kg bw.	[1b]
	Rat:	
	0.5, 2, 5% (500 to 5,000 mg/kg, one month) in diet. Growths effect at 5 %.	[3,10]
	Fisher 344 rats: 0.25, 0.5, 1.0, 2.0 % (250 to 2,000 mg/kg, one month) in diet, males. Enlargement of liver at 2 % doses.	[1]
	Wistar rats: 2% (2 w) in diet, males. Hepatic peroxisome proliferation, increased liver size, enzyme catalase and cartinine acetyltranferase and hypolipidemia	[3]
	0, 0.1, 0.6, 1.2, 2.5% (21 d) in diet. Differences in Bw, in liver weights, kidney weights. Increases in different liver lipids, minor differences between male and females. Dose related increase in peroxisome proliferation at doses above 0.1%, except in female group 0.6 and 1.2% (equivocal).	[3]
	♦700 and 1,500 mg/kg/d (2-year) feeding. Dose related depression of weight gain, NOAEL = 700 mg/kg/d, LOAEL = 1,500 mg/kg/d.	[3,4,21]
	Fisher 344 rats: 1,600, 3,100, 6,300, 12,500, 25,000 ppm (approx. 160-2,500 mg/kg/d; 13-w) oral feeding. NOAEL >12,500 ppm	[1, 4]
	0.16 to 4.7 g/kg/d (90 d) in food. Reduced growth and altered liver and kidney weights in dose groups between 2.9 to 16-4.74 g/kg/d. Death produced at 4.74 g/kg. No effect in animals dosed 0.16 g/kg.	[3]
	♦610-4,760 mg/kg (90 d). NOAEL=610 mg/kg	[1,10,20]
	100 mg/kg (19 months), oral. NOAEL>100 mg/kg	[1,20]
	♦*Fisher 344* rats: 11-2275 mg/kg/d (21 d) Decrease in weight gain, increased liver weight and peroxisome numbers in liver cells above 122 mg/kg bw. NOAEL=122 mg/kg bw.	[1b]
	Dog:	
	2 g/kg (2 month) in diet. Transient loss of appetite.	[3]
Inhalation	No data found	

Dermal	No data found	

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	Mouse: Mutational effect in spermatogenesis and adverse effects in premeiotic stage	[3]
	5 g/kg/d (one or two d) i.p. 6 animals/sex. No significant difference in incidence of polychromatic erythrocytes. Micronucleus test.	[1,3]
	♦0, 0.45, 0.9, 4.6, 9.2 g/kg bw (single dose) intraperitoneal injection to male mice (10/dose), thereafter fertilisation of 2 female/male. Dose related decrease in fertility, dose related increase in dominant-lethal mutations (early foetal deaths). LOAEL was 450 mg/kg bw.	[4,10,22]
	Mouse lymphoma cell: Up to 1,000 nl/ml. Not mutagenic without activation up to 1,000 nl/ml, or at concentration ranging from 15.6 to 250 nl/ml in the presence of activation. Growth parameters was 21.4% at the high dose level in absence of activation and 69.6 to 19.7% at the levels tested in the presence of activation. With and without metabolic activation.	[1,3]
	Drosophila melanogaster: 5,000 ppm (injection) and 20,000 ppm (feeding) male. Canton-S-wild-type males were treated and then mated with 3 harems of virgin females. No sex-linked recessive lethal mutation. 30% mortality in males.	[1,3]
	Salmonella typhimurium: ♦0.025-10.0 mg/plate. Test strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100. Not mutagenic, with or without activation. Preliminary range finding study non-toxic in levels up to 10 mg/plate.	[3,4,10, 32]
	Up to 2 ml of urine from rats dosed 2,000 mg/kg (15d) gavage. Test strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100. No mutagenicity. Modified Ames test, with and without metabolic activator.	[3]
	0.15-150.0 µl/plate. Test strains: TA 1535, TA 1537, TA 1538, TA 98, TA 100. Not mutagenic. Ames Salmonella/Microsome plate test, with or without activation. Preliminary range finding study non-toxic in levels up to 150 µl/plate.	[1,3,10]
	Up to 1000 µg /plate, test strains: TA97, TA98, TA100, TA102. Negative. Ames assay with and without metabolic activation.	[3]

	Saccharomyces cerevisiae: Not mutagenic in test.	[3]
	Rat: Negative, bioassay test	[3]
	No dose specified (single) oral gavage dose, ability of different tumor promoters to DNA synthesis. Test positive, stimulation of DNA synthesis occurred.	[3]
	5-1,000 nl/ml (20-24 h) closed culture vessels. No change in nuclear labelling, slight decrease in relative survival at 1,000 nl/ml dose level (84%). DNA repair assay.	[3]
Chromosome abnormalities	No data found.	
Other genotoxic effects	Human Lymphocytes ♦10, 50, 100 µg/ml. Negative. OECD guideline no. 473, with and without metabolic activation.	[1,10,33]
	CHO cells ♦<400 µg/ml. A weak positive effect without S9 fraction. Not mutagenic with the S9 fraction. With and without metabolic activation system.	[1,10,34]
Other toxic effects	Mouse cell line 3.38, 6.75, 13.5, 27.0 nl/ml in 0.5% acetone (72 h) mouse cell line. No induction change of appearance of number of transformed foci. Cell survival ranged from 89-37.7% relative to control. Cell transformation Assay.	[3]
	0.07, 0.7, 7, 28, 42 nl/ml in 0.5% acetone (48 h) mouse cell line. No induction change of appearance of number of transformed foci. Cell survival ranged from 52.3 to 11.5% relative to control. Cell transformation Assay.	[3]
	0.003, 0.01, 0.1, 0.3 nl/ml in 0.5% acetone (48 h) mouse cell line. No induction change of appearance of number of transformed foci. Cell survival ranged from 99.7 to 43.5% relative to control. Cell transformation Assay.	[3]
Carcinogenicity	Mouse ♦*B6C3F1* mice: 1,800, 3,750 mg/kg/d (103 w) 50 animals/sex/dose group. Carcinogenic to female mice, incidence of hepatocellular liver tumors in female mice. LD_{50}= 47 ml /kg, ip. Carcinogenic bioassay.	[1,3,10, 21]
	♦Test dose not given, oral gavage. $LD_{50,}$ male =15 g/kg. Carcinogenic bioassay.	[3]
	Test dose not given, oral gavage. $LD_{50,}$ female =25 g/kg. Carcinogenic bioassay.	[3,21]
	B6C3F1 mice: 0, 12,000, 25,000 ppm (104 w) oral in diet. Test substance related liver carcinoma or adenoma observed.	[3] [4]

	Rat	
	LD_{50}=0.9 ml/kg, i.v. Carcinogenicity bioassay.	[3,21]
	LD_{50}=5.6 g/kg, oral. Carcinogenicity bioassay.	[3]
	LD_{50}=47 ml/kg, ip. Carcinogenicity bioassay.	[3]
	$LD_{50,}$ male =45 g/kg, oral gavage. Carcinogenicity bioassay.	[3]
	$LD_{50,}$ female =25 g/kg, oral gavage. Carcinogenicity bioassay.	[3]
	Male *Wistar* rats: Hepatic microsomal lauric acid hydroxylase activity and peroxisome proliferation in liver, phenobarbital and 3-methylcholanthrene total cytochrome P450 was 1.7-2.7 times induced.	[3]
	Fisher 344 rats: 1.2, 2.5, 1.5%, to males in diet. Significant increase in 8-hydroxydeoxyguanosine levels in liver after 1 and 2 weeks of treatment. Indicates involvement of oxidative DNA damage in hepatocarcinogenesis by peroxisome proliferation.	[3]
	Fisher 344 rats: 0, 12,000, 25,000 ppm (103 w) oral in diet. Test substance related liver carcinomas or adenomas were not observed.	[4]
	♦*Fisher 344* rats: 600, 1,250 mg/kg/d (103 w) oral feed 1-3 times/w, 50 animals/sex. Not potentially carcinogenic to rats.	[1,10,21]
	Mouse and rat	
	♦*Fisher 344* rats and *B6C3F1* mice: 2.5 g/kg/d. Dose related increase in liver weight, palmitoyl CoA oxidation markedly increased, some glycogen loss, dose-related hypertrophy, increased eosinophilia in both mice and rats, peroxisome proliferation combined with reduction of lipid in the centrilobar hepatocytes. Indication of higher sensitivity for rats than mice to hepatic peroxisome proliferation due to DEHA. No dose specified (2 year). Hepatocarcinogenesis in female mice.	[3]
	Male *Fisher 344* rats and female *B6C3F1* mice: 2 g/kg (14 d). Significant increase in perixomal-acyl-CoA and catalase, decrease in glutathione peroxidase in rats and mice. Increase in steady state hydrogen concentration in liver homogenates.	[3,35]
	Fisher 344 rats and female *B6C3F1* mice: 12,000 and 25,000 ppm (103 w) oral, 50 animals per dose group. Decrease in BW in high dose groups. Not carcinogenic.	[3,4]
	Carcinogenic to rats. Carcinogenic to mice, especially female mice. Dose related occurrence of adenomas and hepatocellular carcinomas in mice, significant in males in high dose group and in females in low and high dose groups. Carcinogenic bioassay.	[3,4]
Cancer Review	IARC - Not classifiable as a human carcinogen. Limited evidence of carcinogenicity in animals.	[6]

Diethylhexyl adipate

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity/teratogenicity	Many studies present.	
	Mouse: Test dose not given, single IP doses to males, mated with untreated females. Dose-dependent antifertility, dominant lethal mutation indicated by reduced the % of pregnancies and increased number of early foetal deaths.	[3,4]
	Rat: ♦*Alpk:APfSD* rats: 0, 300, 1,800, 12,000 ppm (28, 170 1,080 mg/kg/d; 10 w). No treatment related effects on male or female fertility. Fertility study (OECD 415/1988). NOAEL, parental= 1,800 ppm, NOAEL, F0 offspring= 1,800.	[46]
	♦*Alpk:APfSD* rats: 0, 28, 170, 1080 mg/kg/d, 24 pregnant females/dose, in diets on gestation days 1-22. Changes in maternal bw gain, and food consumption, reduced ossification, Kinked and dilated uterus in foetuses, developmental study (OECD 414/1981). NOAEL (foetotoxicity) = 28 mg/kg bw/d. Not significant.	[4,10]
	♦*Sprague Dawley* rats: 0.9, 4.6, 9.2 g/kg (on day 5, 10 and 15 of gestation) i.p. 5 pregnant rats. Reduced foetal weight in dose groups 4.6 and 9.6 g/kg. Developmental/teratogonicity study. NOAEL (maternal toxicity) = 0.9 g/kg bw/d, NOAEL (teratogenicity) = 0.9 g/kg bw/d (higher values in ref. [46]).	[4,10]

Toxicokinetics

Toxicokinetics	Rat: ♦*In vivo* - different doses of DEHA and mono-(2-ethylhexyl)-adipate (5d) gavage, *in vitro* – hepatocytes. No DEHA in urine after 24 h. Adipic acid was main metabolite, 2-ethylhexanol pathway showed further metabolites, mainly 2-ethylhexanoic acid which was conjugated or submitted to other pathways, 2-ethylhexanoic acid glucoronidation appeared dose and time dependent, 2-ethylhexanol glucoronidation was more stable. *In vitro*, first hydrolysis of DEHA a rate limiting step, when adding mono-(2-ethylhexyl)adipate all *in vivo* metabolites were found, Glucoronidation of 2-ethylhexanol and 2- ethylhexanoic acid was dose and time dependent.	[3,38]

	Mouse, rat, guinea pig, marmoset: ♦Up to 5 mM, metabolites of DEHA, potential as peroxisome proliferators. In mice mono(2-ethylhexyl)adipate and 2-ethylhexanol equipotent in inducing oxidation, 2-ethylhexanoic acid increased oxidation by 25 fold at 1mM, other metabolites smaller increases in oxidation. Concentration of respectively 2-ethylhexanoic acid, 2-ethylhexanol and mono(2-ethylhexyl)adipate above 1mM resulted in cytotoxic signs (blebbing, rounding of cells, detachment from the cultured flasks). No peroxisomal beta-oxidation at up to 5 mM DEHA in rats hepatocytes and at up to 2 mM in guinea pig or marmoset hepatocytes.	[3,39]
	Mouse and rat: Test dose unspecified, 14C-labelled (carbonyl or alcohol moiety) DEHA (once) on day 17 of gestation, male rats, male mice and pregnant female mice, i.v., in dimethyl sulfoxide and intragastrically. Distribution highest in body fat, liver, kidney when administered i.v. or intragastrically, 14C activity in bronchi of male mice (alcohol labelled), in pregnant mice DEHA observed in foetal liver, intestine, bone marrow during the first 24 h when carbonyl labelled. Very little in mice foetuses when alcohol labelled. No DEHA in mice after 4 d. Blood DEHA in rats 2-3 times higher when given in DMSO than in corn oil. Sign. amount of DEHA excreted in bile in rat when treated with DEHA in DMSO, alcohol labelled. DEHA excreted in urine, vehicle little effect on amount excreted. DEHA poorly absorbed from an oil solution.	[3]
	Intestinal homogenates from rats: Hydrolysis was rapid, estimated half-life of 6.0 min.	[3]

Ecotoxicity Data

Algae	*Selenastrum capricornutum:*	
	EC_{50}(72h)>500 mg/l, EPA-600/9-78-018	[1]
	EC_{50}(96h)> 100×S_w, EPA-test	[10]
	♦LC_{50}(96h)=0.78 mg/l	[11,18]
	Scenedesmus subspicatus:	
	EC_{50}(72h)>500 mg/l, DIN 38412/11	[10,16]
	EC_{50}(72h)=400 mg/l, DIN 38412/11	[10]

Diethylhexyl adipate

Crustacean	*Daphnia magna* (fw):	
	EC_{50}(24h)>1000 mg/l	[15]
	EC_{50}(24h)>500 mg/l, Dir. 84/449/EEC	[1]
	EC_{50}(24h)>2.1 mg/l, DIN 38412/11	[1]
	EC_{50}(24h)>500 mg/l, OECD 202	[10,16]
	EC_{0}(24h)=500 mg/l, OECD 202	[10]
	EC_{50}(48h)>500 mg/l, Dir. 84/449/EEC	[1]
	EC_{50}(48h)>500 mg/l, OECD 202	[10]
	LC_{50}(48h)=0.66 mg/l (range: 0.48-0.85 mg/l)	[11]
	♦EC_{50}(48h)=0.66 mg/l, EPA-66013-75-009	[18]
	EC_{0}(48h)=250 mg/l, OECD 202	[10]
	EC_{50}(96h)= 0.66 mg/l, EPA-66013-75-009	[1,10]
	♦NOEC(96h)<0.32 mg/l, EPA-6603-75-009	[1,10,18]
	MATC(21d)=0.024-0.052 mg/l (geometric mean 0.035 mg/l), Reproduction test according to ASTM E 47.01	[1,11,10, 18]
	Chaetogammarus marinus (sw):	
	LC_{0}(96 h)=100 mg/l	[10]
	Nitocra spinipes (sw):	
	LC_{100}(96 h)<100 mg/l	[10]
Fish	*Lepomis machrochirus* (fw):	
	♦LC_{50}(96h) >100×sol_{w}, EPA-66013-75-009	[18]
	Onchorhynchus mykiss (fw):	
	LT_{50}(96h)=110 mg/l	[10]
	♦LC_{50}(96h) >100× sol_{w}, EPA-66013-75-009	[18]
	EC_{50}(96h)=54-150 mg/l	[16]
	Pimephales promelas (fw):	
	♦LC_{50}(96h) >100× sol_{w}, EPA-66013-75-009	[1,10,18]
	Poecilia reticulata (fw):	
	LC_{50}(96h)>100× sol_{w}	[10]
	Salmo gairdneri (fw):	
	LC_{50}(72h)>1 mg/l	[1,10]
	LC_{50}(96h)=54-150 mg/l	[1,15]
	LC_{50}(96h)>100× sol_{w}, EPA-66013-75-009	[1]
Bacteria	*Pseudomonas putida*:	
	EC_{50}>10,000 mg/l, DIN 38412	[1,15,16]
	Inhibition of activated sludge:	
	EC_{20}>350 mg/l , OECD 302C/209	[16]
Terrestrial organisms	No data found	
Other toxicity information	No data found	

Diethylhexyl adipate

Environmental Fate

BCF	2700 (estimated) 2264 (estimated) 2692 (estimated)	[1] [8] [10]
	Lepomis macrochirus (fw): ♦27 (28d, measured)	[2,10,16, 18]
Aerobic biodegradation	Aquatic – ready biodegradability tests: ♦66 % at 100 mg/l in 28 d, OECD 301 C ♦68 % at 100 mg/l in 28 d, OECD 301 C <60 % in 28 d, OECD 301 C ♦>98% in 28 d, OECD 301 F ♦93.8 at 20,1 mg/l in 35 d, Modified Sturm-Test >60% in 28 d (OECD 301) 67-74 % at 100 mg/l in 28 d, OECD 301 C	 [1,10,42] [1,10,43] [1] [10,44] [1,9,10,44 [15,16] [17]
	Aquatic – other tests: 65-81 % in 1 d, SCAS 88-96 % in 1 d, SCAS Ca. 73 % at 20 mg/24h. in 1 d, SCAS Ca. 92 % in at 5 mg/24h. in 1 d, SCAS 81.6 % at 37.4 mg/l in 35 d, Shake-flask-system 94% after 35 d, Sturm-test 94 % in 35 d 81.6 % in 14 d, 14 d die-away test	 [1,10] [1,10] [1,8,9,10] [1,8,9,10] [1,9,10] [1] [3,10] [8]
	Terrestrial environment: > 50 % in 30 d, Sandy loam	 [10]
Anaerobic biodegradation	No data found	
Metabolic pathway	No data found	
Mobility	K_{oc}=50,468	[10]

Conclusion

Physical-chemical	Reviewed data on diethylhexyl adipate (DEHA) indicates that the substance is non-volatile and non-flammable compound with low water solubility. Further the available data on $LogP_{ow}$ indicates strong lipophilicity and partitioning to particles and biota. DEHA has a migration potential in PVC films, which in several cases exceeds the Danish limit of 4 mg/dm^2.

Diethylhexyl adipate

Emission	DEHA is according to the available estimates released during production. Concentrations
Exposure	DEHA has been found in the aquatic environment and in drinking water. DEHA has also been found to migrate in food, which has been in contact with cling films, Patients treated using plastic tubing, which has been produced using DEHA, could be exposed to DEHA.
Health	LD_{50} was 7,392 mg/kg bw in rat in acute oral tests. Acute effects were not observed from DEHA in inhalation studies nor was DEHA shown to be sensitising. DEHA was slightly irritating to skin and eyes. The subacute NOAEL was 610 mg/kg bw in rat and more than 3,100 ppm in mouse. DEHA was only slightly mutagenic in *in vitro* tests. Studies on dominant lethal mutations in mouse showed a LOAEL on 450 mg/kg bw. Metabolites showed no mutagenic effects in Ames tests with *Salmonella typhimurium*. DEHA shows limited evidence of carcinogenicity in animals (IARC, group 3). NOAEL was 1,200 ppm for both the parent and the F_0 generation in reproductive toxicity studies on mouse. The NOAEL was 170 mg/kg/d and LOAEL was 1,080 mg/kg/d to rat in reproductive toxicity tests. Critical effect: NOAEL, foetotoxicity was 28 mg/kg bw/d. In rat adipic acid was the main metabolite. In human blood the main metabolite was 2-ethylhexane acid. The metabolites 2-ethyl-5-hydroxyhexane acid, 2-ethyl-5-ketohexane acid, 2-ethyl-1,6-hexandiacid were found in human urine and di-(2-ethylhexyl)adipate and mono-(2-ethyl-hexyl)adipate were found in human faeces. Elimination half-life of DEHA was only 1½ hour. Distribution of DEHA was highest in body fat, liver and kidney when administered once intravenous or intragastrically to mouse and rat. No DEHA was observed in mouse after 4 days.
Environment	According to the available biodegradation data there is good evidence of ready biodegradability of DEHA. In one study DEHA is very toxic to *D. magna* with 50% mortality slightly below 1 mg/l. The available ecotoxicological data on DEHA from several other experiments show no mortality in algae, crustaceans, and three fish species at concentrations up to 100 times the water solubility of DEHA. The maximum acceptable toxicant concentration in a chronic test on reproduction in *D. magna* was 0.024-0.052 mg/l. Bioaccumulation was 27 in test with bluegills, 100 times less than predicted from $LogP_{ow}$.

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O-acetyltributyl citrate

CAS number: 77-90-7

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

Indications are available that O-acetyltributyl citrate is non-volatile and non-flammable compound with low water solubility. Further the available data indicates that this compound bioaccumulates. ATBC will migrate from cling film to food.

Emission

No data found.

Exposure

Human occupational exposure may occur through inhalation of dust particles and dermal contact when working at places where O-acetyl tributyl citrate is handled. General exposure of the population may occur through dermal contact with consumer products containing O- acetyl tributyl citrate and ingestion of contaminated food.
O-acetyl tributyl citrate has been found in the aquatic environment.

Health

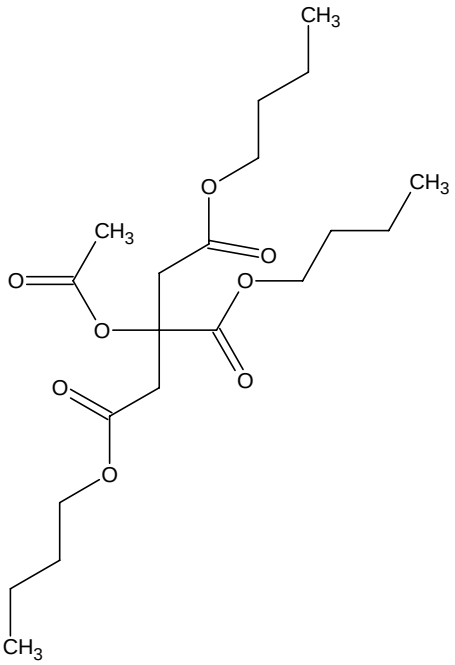
Sufficient data were not found.
LD_{50} to rat was 31,4 g/kg in acute tests which indicated very low toxicity. O-acetyl tributyl citrate was not found to be irritant to skin or sensitising. Moderate eye irritation has been observed. O-acetyl tributyl citrate was not mutagenic and did not cause chromosomal aberrations in rat lymphocytes or unscheduled DNA synthesis in rats treated by gavage. The negative UDS study indicated that the in vivo genotoxic potential of ATCB is low or absent
The carcinogenic potential could not be evaluated from the reviewed study. Decreased body weights were observed in a 2-generation study (NOAEL 100 mg/kg bw/day). Based on limited data available the critical effect appears to be reproductive toxicity and repeated dose toxicity.
Sufficient data are not available to evaluate the classification of the substance for all effects (EU, 1967).

Environment

Only ecotoxicological data for fish were found. Acute mortality in two freshwater fish were 38-60 mg/l. According to the available biodegradation data there is no evidence of ready biodegradability of ATBC.

O-acetyltributyl citrate

Identification of the substance

CAS No.	77-90-7
EINECS No.	201-067-0
EINECS Name	Tributyl O-acetylcitrate
Synonyms	1,2,3-Propanetricarboxylic acid, 2-(acetyloxy)-tributyl ester; acetyl tri-n-butyl citrate, acetylcitric acid tributyl ester, blo-trol, citric avid tributyl ester acetate, citroflex A, citroflex A 4, tributyl acetylcitrate, tributyl 2-acetoxy-1,2,3-propanetricarboxylate, tributyl acetylcitrate, tributyl O-acetylcitrate, tributyl 2-(acetyloxy)-1,2,3-propanetricarboxylic acid, tributyl acetate
Molecular Formula	$C_{20}H_{34}O_8$
Structural Formula	
Major Uses	Flavour ingredient [3] Plasticiser for vinyl resins, rubber and cellulosic resins [3] Plasticiser for cellulose nitrate, ethyl cellulose, polystyrene acetate, polyvinylchloride, vinylchloride copolymers [3]
IUCLID	The substance is not included in the IUCLID HPVC list.
EU classification	The compound is not included in Annex I to 67/548/EEC

O-acetyltributyl citrate

Physico-chemical Characteristics

Physical Form	Colourless liquid	[3,6]
Molecular Weight (g/mole)	♦402.48 402.88	[1] [3]
Melting Point/range (°C)	♦-80	[3,6]
Boiling Point/range (°C)	172-174 °C at 1 mm Hg	[1,3,6]
Decomposition Temperature (°C)	No data found	
Vapour Pressure (mm Hg at °C)	♦1 at 173 °C ♦4.6×10^{-6} (estimated) 1 5.2×10^{-2}	[3] [3] [6] [16]
Density (g/cm^3 at °C)	1.05 1.046 at 25°C 1.048	[1] [3] [6]
Vapour Density (air=1)	No data found	
Henry's Law constant (atm/m^3/mol at °C)	3.8×10^{-6} (estimated, unknown temperature)	[3]
Solubility (g/l water at °C)	♦0.005 (unknown temperature) Insoluble in water (unknown temperature)	[3] [6]
Partition Coefficient (log P_{ow})	♦4.31 (estimated)	[3]
pK_a	Not applicable	
Flammability	No data found	
Explosivity	No data found	
Oxidising Properties	No data found	
Migration potential in polymer	Household cling film: Sunflower oil (10d, 40 °C)=4.7 mg/dm^2 Acetic acid (10d, 40 °C)=2.8 mg/dm^2 Migrated amount to cheese was 1-6% of plasticiser amount in film corresponding to 0.1-0.7 mg/dm^2. PVC transfusion tubing: Studies on the migration potential of O-acetyltributyl citrate has shown that O-acetyltributyl citrate is ex-	[15] [15] [20] [17]

	tractable from PVC tubing using distilled water as a solvent. Extraction studies of Poretex PVC transfusion tubing resulted O-acetyltributyl citrate concentrations after 2 h. of 100 µg/l. Perfusion studies of the same PVC tubing resulted in an average O-acetyltributyl citrate concentrations (mean of extract concentration after 2-10 h. extraction) of ~6 µg/l.	

Emission Data

During production	No data found	

Exposure Data

Aquatic environment, incl. sediment	O-acetyltributyl citrate was found in 2 water samples taken from River Lee (UK) at trace levels.	[3]
Terrestrial environment	No data found	
Sewage treatment plant	No data found	
Working environment	No data found	
Consumer goods	No data found	
Man exposed from environment	No data found	
”Secondary poisoning”	No data found	
Atmosphere	No data found	
Dermal	No data found	

Toxicological data

Observations in humans	No evidence of sensitisation and irritation in a sensitisation test.	[22]

O-acetyltributyl citrate

Acute toxicity

Oral	Rats and cats Single oral doses, 10-30 ml/kg. No marked effect observed.	[3]
	♦Rat LD_{50}=31.4 g/kg	[3]
Dermal	No data available	
Inhalation	No data available	
Other routes	♦Rabbit Local anaesthetic action.	[3]
	Blocks neural transmission in rats when placed in contact with a nerve trunk.	[3]
	0.1 g/kg i.v. caused increased motor activity and respiration. Unspecified dosed had a depressive effect on the blood pressure.	[21]
	♦Mouse and rat 0.4 g/kg increased respiration and induced severe signs of central nervous system toxicity.	[21]
Skin irritation	♦Rabbit Not a skin irritant.	[22]
Eye irritation	♦Rabbit 5% suspension instilled in the eye caused temporarily abolished corneal reflex action.	[21]
	♦Rat Moderate eye irritation.	[22]
Irritation of respiratory tract	No data available	
Skin sensitisation	♦Guinea pig Not a sensitiser in guinea pig maximisation test.	[22]

O-acetyltributyl citrate

Subchronic and Chronic Toxicity

Oral	Rats 5 or 10% in the diet (6-8 w) in male rats. The lower dose had no deleterious effect on growth whereas the high dose produced frequent diarrhoea and markedly depressed growth.	[21]
	1000 (1%), 2,700 (2.5%) and more mg/kg bw/d in the diet (4 w). Decreased body weights and changes in organ weights from 2.5% onwards. No effects at 1%. Range finding study.	[22]
	♦100, 300, 1,000 mg/kg bw/d (90 d) in *Wistar* rats. Haematological and biochemical changes from 300 mg/kg bw/d. Increased lever weights at 1,000 mg/kg bw/d. NOAEL 100 mg/kg bw/d. (OECD 408)	[22]
Inhalation	No data available	
Dermal	Mice 900 mg/kg (14 d), i.p. No other effects than decreased red blood cell count were observed.	[3]

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	*Salmonella typhimurium* ♦No dose mentioned. Not mutagenic.	[5]
Gene Mutation	♦Not mutagenic	[3]
	Mouse lymphoma No dose mentioned. Test strain: L5178Y. No gene mutations were observed. Suspension/plate with and without metabolic activation.	[5]
	Salmonella typhimurium ♦No dose mentioned, test strain: TA98, TA100, TA 1535, TA1537 and TA1538. No gene mutations were observed. Standard plate with metabolic activation). Ames test.	[5]
Chromosome Abnormalities	Rats ♦Single doses by gavage of 800 or 2,000 mg/kg did not produce unscheduled DNA systhesis.	[22]
	Rat lymphocytes ♦Dose levels not reported. No chromosomal aberrations were observed in the absence or presence of activation.	[22]

O-acetyltributyl citrate

Other Genotoxic Effects	Human KB cells: 50% inhibited growth= 44.7 µg/Ml	[3]
	Monkey Vero cells: 50% inhibited growth = 39.9 µg/mL	[3]
	Canine MDCK cells: 50% inhibited growth = 42.1 µg/mL	[3]
	Rat liver microsomes: Laurate 12-hydroxylase activity in acetyl-tributyl-citrate rats = 4,4 nmol (controls = 2.8 nmol). Cyto-chrome p450-mediated fatty acid omega-hydroxylation system.	[3]
Carcinogenicity	♦Rat (Sherman) 0, 200, 2000, 20000 ppm (1000 mg/kg bw/d) (2 years). No significant findings. Not according to modern guidelines. ATBC not a potent multi-site carcinogen.	[22]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat, Sprague Dawley ♦0, 100, 300, 1000 mg/kg bw/d in the diet. 2-generation reproduction study (OECD 416). Decreased body weights in F1 males from 300 mg/kg bw/d and F0 males at 1000 mg/kg bw/d- NOAEL 100 mg/kg bw/d.	[22]
Teratogenicity	No data found	
Other Toxicity Studies	No data found	
Toxicokinetics	ATBC is rapidly absorbed after oral administration. Half-life = 1 hour. >67% is absorbed and primarily ex-creted into urine (approx. 64%). Excretion in faeces amounts to approx. 32% and 2% in air.	[22]

Ecotoxicity Data

Algae	No data found	
Crustacean	No data found	
Fish	*Lepomis macrochirus* LC_{50} (96h) = 38-60 mg/l	[23]
	Fundalus heteroclitus LC_{50} (96h) = 59 mg/l	[23]

Bacteria	No data found
Terrestrial organisms	No data found
Other toxicity information	No data found

Environmental Fate

BCF	♦1,100 (estimated)	[18]
Aerobic biodegradation	Aquatic – other tests: 80 % at 30 mg/l in 28 d, modified MITI Test	[19]
Anaerobic biodegradation	No data found	
Metabolic pathway	No data found	
Mobility	K_{oc}≈5100 (estimated)	[3]

Conclusion

Physical-chemical	Indications are available that O-acetyltributyl citrate is non-volatile and non-flammable compound with low water solubility. Further the available data indicates that this compound bioaccumulates.
Emission	No data available
Exposure	Human occupational exposure may occur through inhalation of dust particles and dermal contact when working at places where O-acetyl tributyl citrate is handled. General population exposure may occur through dermal contact with consumer products containing O- acetyl tributyl citrate and ingestion of contaminated food. O-acetyl tributyl citrate has been found in the aquatic environment.

O-acetyltributyl citrate

Health	Sufficient data were not found. LD_{50} to rat was 31,4 g/kg in acute tests. O-acetyl tributyl citrate was not found to be irritant to skin or sensitising. Moderate eye irritation has been observed. O-acetyl tributyl citrate was not mutagenic and did not cause chromosomal aberrations in rat lymphocytes or unscheduled DNA synthesis in rats treated by gavage. The negative UDS study indicated that the in vivo genotoxic potential of ATCB is low or absent The carcinogenic potential could not be evaluated from the reviewed study. Decreased body weights were observed in a 2-generation study (NOAEL 100 mg/kg bw/d). Based on limited data available, the critical effect appears to be reproductive toxicity and repeated dose toxicity. Sufficient data are not available to evaluate the classification of the substance for all effects (EU, 1967).
Environment	According to the available biodegradation data there is no evidence of ready biodegradability of O-acetyltributyl citrate. Acute mortality in two freshwater fish were 38-60 mg/l.

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http://toxnet.nlm.nih.gov

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Di(2-ethylhexyl) phosphate

CAS number: 298-07-7

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

Di(2-ethylhexyl) phosphate is a slightly flammable compound when exposed to heat. It has a low water solubility and vapour pressure.

Emission

No data found

Exposure

No data found

Health

Inhalation of 2 ppm caused weakness, irritability and headache in humans.
Acute oral toxicity (LD_{50}) of di(2-ethylhexyl) phosphate to rat was 4,940 mg /kg bw whereas the LD_{50} in an acute dermal application test on rat was 1,200 mg/kg bw. The i.p. LD_{50} for rat was 1,200 mg/kg bw.
Di(2-ethylhexyl) phosphate exhibit strong corrosive effect in cornea at 5 µl doses (1% solution) as well as skin irritating effects. No mutagenic activity has been observed.

All endpoints have not been sufficiently investigated. Dermal toxicity and local corrosive effects on skin and eyes seems to be the most severe effects. Sufficient data are not available for classification. DEHPA has been classified by Bayer AG in 1993 as C (*Corrosive*); R34 (*Causes burns*) and Xn (*Harmful*); R21 (*Harmful in contact with skin.*

No data found to determine reproductive toxicity or teratogenicity.

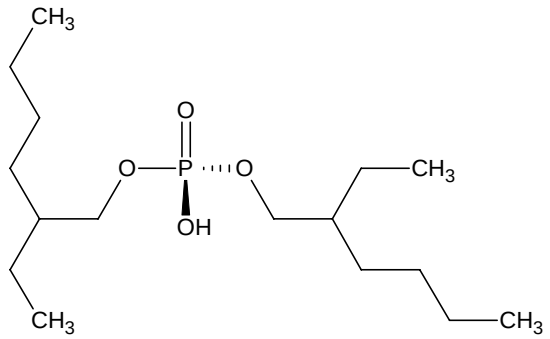
Environment

Conflicting data on the biodegradability of di(2-ethylhexyl) phosphate are available. The compound is here evaluated as inherently biodegradable.

The BCF values indicates that di(2-ethylhexyl) phosphate does not bioaccumulate.
The available ecotoxicological data indicates that di(2-ethylhexyl) phosphate is harmful to algae, crustaceans and fish.

Di(2-ethylhexyl) phosphate

Identification of the substance

CAS No.	298-07-7	
EINECS No.	206-056-4	
EINECS Name	Bis(2-ethylhexyl) hydrogen phosphate	
Synonyms	Bis(2-ethylhexyl) hydrogenphosphate, Bis(2-ethylhexyl) orthophosphoric acid, Bis(2-ethylhexyl) phosphoric acid, D2EHPA, DEHPA, DEHPA extractant, Di-(2-ethylhexyl) acid phosphate, Di-2-ethylhexyl hydrogen phosphate, Di-(2-ethylhexyl) phosphoric acid, Di(2-ethylhexyl) orthophosphoric acid, Di(2-ethylhexyl) phosphate, Di-(2-ethylhexyl) phosphoric acid, ECAID 100, 2-ethyl-1hexanol hydrogen phosphate, HDEHP, hydrogen bis(2-ethylhexyl) phosphate, phosphoric acid bis(ethylhexyl) ester, phosphoric acid bis(2-ethylhexyl) ester.	
Molecular Formula	$C_{16}H_{35}O_4P$	
Structural Formula		
Major Uses	Additive to lubrication oils, corrosion inhibitors and antioxidants.	[3]
	Metal extraction and separation.	[3]
	Intermediate for wetting agents and detergents.	[3]
	Extraction of drugs from aqueous phase.	[3]
IUCLID	The compound is not listed as HPVC.	
EU classification	The compound is not included in Annex I to 67/548/EEC	[10]

Physico-chemical Characteristics

Physical Form	Colourless Liquid	[3,15]
Molecular Weight (g/mol)	322.48	[3]

Di(2-ethylhexyl) phosphate

Melting Point/range (°C)	-60 °C ~50 °C	[3] [15]
Boiling Point/range (°C)	♦48 at 12 mm Hg Decomposition occurs prior to boiling	[1] [10]
Decomposition Temperature (°C)	240	[10]
Vapour Pressure (mm Hg at °C)	♦4.65×10^{-8} (estimated) < 0.003	[3] [15]
Density (g/cm^3 at °C)	0.97 0.96 at 20 °C	[1] [10,15]
Vapour Density (air=1)	No data found	
Henry's Law constant ($Pa/m^3/mol$ at °C)	4.16×10^{-3} (estimated)	[3]
Solubility (g/l water at °C)	0.1 (20 °C)	[3]
Partition Coefficient (log P_{ow})	6.07 (estimated) ♦2.67, MITI	[3] [10]
pK_a	♦1.72 (estimated) 2.17 (estimated)	[10] [10]
Flammability	♦Slightly flammable when exposed to heat.	[3]
Explosivity	May form flammable hydrogen gas.	[3]
Oxidising Properties	No data found	
Migration potential in polymer	No data found	

Emission Data

During production	No data found

Exposure Data

Aquatic environment, incl. sediment	No data found
Terrestrial environment	No data found
Sewage treatment plant	No data found

Di(2-ethylhexyl) phosphate

Working environment	No data found concerning concentration in the working environment. Potential working groups to be exposed: workers in the radiochemical industry where bis(2-ethylhexyl) hydrogen phosphate is used to extract radioactive metals; workers using bis(2-ethylhexyl) hydrogen phosphate during manufacture of certain lubricating oils, wetting agents and detergents.	[3]
Consumer goods	No data found	
Man exposed from environment	No data found	
”Secondary poisoning”	No data found	
Atmosphere	No data found	
Dermal	Bis(2-ethylhexyl) hydrogen phosphate is a liquid used for the extraction of heavy metals as an additive for lubricating oil and as an intermediate for manufacture of wetting agents and detergents, the most probable route of exposure is by skin absorption.	[3]

Toxicological data

Observations in humans	♦Smarting of skin and first degree burns on short exposure. May cause second degree burn on long term exposure. Irritating to skin and eyes.	[3]
	♦Inhalation of 2 ppm caused weakness, irritability and headache.	[3]

Acute toxicity

Oral	Rat:	
	♦LD_{50}=4,742 mg/kg	[10]
	LD_{50}=4,940 mg/kg	[10]
Dermal	Rabbit:	
	♦LD_{50}=1,200 mg/kg bw (1.25 ml/kg; 24 h)	[10]
	LD_{50}=1,250 mg/kg bw	[3]
Inhalation	Rat:	
	Saturation concentration < 1,300 mg/m^3	[10]
	Dogs:	
	♦8 hours exposure of 380 ppm caused death.	[3]

Other routes	Mouse: I.p. study. LD_{50}= 62.5 mg/kg bw	[10]
	Rat: ♦I.p. study. LD_{50}= 50-100 mg/kg, 50% mortality was observed in dose group 500 mg/kg bw. Adhesion in inner organ of animals from the 50 mg/kg bw group. I.p. study. LD_{50} varied between less than 50 mg/kg to more than 5,000 mg/kg.	[10] [3]
Skin irritation	♦10 µL undiluted (24 h), 5 animals. Necrosis was observed after 24 h. Intact skin, occlusive test. 500 µl (4-8 h).	[10] [10]
Eye irritation	Rabbit: 100 µl, 2 young animals, application in eye. Corrosive to cornea and irritating to mucous membrane. ♦5 µl (1% solution) young animals. Strong corrosive effects in cornea.	[10] [10]
Irritation of respiratory tract	No data found	
Skin sensitisation	No data found	

Subchronic and Chronic Toxicity

Oral	Rat: ♦*Sprague Dawley* rats: 0.25%, 1%, 3% (25, 100, 200 mg/kg bw) (5 d), feed. Significant increases in the relative liver weight in the 1% and 3% dose groups. Test substance was a potent inductor of the P450b+e system. Mouse: *C57B1/6*: 1,500 mg/kg bw (4 d), 3 animals. Significant increases in liver weights. Increases in the perixomale enzymes carnitine acetyltranferase and palmitoyl CoA-oxidase.	[10] [10]
Inhalation	No data found	
Dermal	No data found	

Di(2-ethylhexyl) phosphate

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	*Salmonella typhimurium:* ♦4-2,500 µg/plate, strain: TA98, TA100, TA1535, TA1537, all strain tested both with and without metabolic activation. No mutagenicity was observed.	[10]
	0.001-5 µl/plate, strain: TA98, TA100, TA1535, TA1537, TA1538, all strain tested both with and without metabolic activation. No mutagenicity was observed.	[10]
	Saccharomyces cerevisiae: 0.001-5 µl/plate. Tested both with and without metabolic activation. No mutagenicity was observed.	[10]
	Mouse lymphoma: 0.05 - 0.095 µl/ml. No metabolic activation. No mutagenicity was observed.	[10]
Gene Mutation	No data found	
Chromosome Abnormalities	No data found	
Other Genotoxic Effects	No data found	
Carcinogenicity	No data found	

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	No data found
Teratogenicity	No data found
Other Toxicity Studies	No data found

Toxicokinetics

Toxicokinetics	No data found

Ecotoxicity Data

Di(2-ethylhexyl) phosphate

Algae	*Chlorella emersonii:*	
	Growth inhibition at conc.= 0.3-100 mg/l	[3]
	♦EC_{50}(48h)=50-100 mg/l	[10]
Crustacean	*Daphnia magna:*	
	EC_{50}(24h)=42.0 mg/l	[11]
	LC_{50}(24h)>42 mg/l	[10]
	♦EC_{50}(48h)=42.0 mg/l	[11]
	♦EC_{50}(48h)=60.7 mg/l	[11]
	♦EC_{50}(48h)=75.0 mg/l	[11]
	♦EC_{50}(48h)=76.9 mg/l	[11]
	♦EC_{50}(48h)=83.7 mg/l	[11]
	♦LC_{50}(48h) > 42 mg/l	[10]
	EC_{50}(72h)=24.5 mg/l	[11]
	EC_{50}(72h)=29.0 mg/l	[11]
	EC_{50}(72h)=30.2 mg/l	[11]
	EC_{50}(72h)=40.2 mg/l	[11]
	EC_{50}(72h)=46.8 mg/l	[10]
	EC_{50}(72h)=47.4 mg/l	[11]
	EC_{50}(72h)=47.9 mg/l	[11]
	LC_{50}(72h)=36.5 mg/l	[11]
	LC_{50}(72h)=46.8 mg/l	[11]
	EC_{50}(96h)=11.1 mg/l	[11]
	EC_{50}(96h)=12.1 mg/l	[11]
	EC_{50}(96h)=18.4 mg/l	[11]
	EC_{50}(96h)=26.0 mg/l	[11]
	EC_{50}(96h)=27.2 mg/l	[11]
	EC_{50}(96h)=28.7 mg/l	[11]
	EC_{50}(96h)=28.2 mg/l	[11]
	LC_{50}(96h)=16.5 mg/l	[10]
	LC_{50}(96h)=27.2 mg/l	[10]
Other invertebrates	No data found	
Fish	*Salmo gairdneri* (fw)*:*	
	Inhibited growth at conc.= 0.3-100 mg/l	[3]
	♦LC_{50}(96h)=48-54 mg/l	[10]
	Oncorhynchus mykiss (fw):	
	LC_{50}(48h)=22-43 mg/l	[10]
	♦LC_{50}(96h)=20-36 mg/l	[10]
	LC_{50}(120h)=20-34 mg/l	[10]
	Danio rerio (fw)*:*	
	♦LC_{50}(96h)=56 mg/l	[11]

Di(2-ethylhexyl) phosphate

Bacteria	*Pseudomonas flourescens*: EC_0(48h)=2,340 mg/l, DEV L8	[10]
	Thiobacillus ferooxidans: IC_{68}(3h)=443 mg/l, respiration	[10]
	Cellulomonas and sporocytophaga myxococcoides: Inhibited growth at conc.= 0.3-100 mg/l	[3]
Terrestrial organisms	No data found	
Other toxicity information	No data found	

Environmental Fate

BCF	37 (estimated) *Cyprius carpio* (fw): ♦1.1-6, MITI test	[10] [10]
Aerobic biodegradation	Aquatic – ready biodegradability tests: ♦ 75 % at 100 mg/l in 28 d, modified MITI Test	[9,10,15]
	Aquatic – other tests: ♦0-17 % at 30 mg/l in 28 d, modified MITI Test	[10]
Anaerobic biodegradation	No data found	
Metabolic pathway	No data found	
Mobility	No data found	

Conclusion

Physical-chemical	Di(2-ethylhexyl) phosphate is a slightly flammable compound when exposed to heat with a low water solubility and vapour pressure.
Emission	No data found
Exposure	No data found

Di(2-ethylhexyl) phosphate

Health	Inhalation of 2 ppm caused weakness, irritability and headache in humans. Acute oral toxicity to rat expressed as LD_{50} was 4,940 mg di(2-ethylhexyl) phosphate /kg bw and the LD_{50} in an acute dermal application test on rat was 1,200 mg di(2-ethylhexyl) phosphate/kg bw. The i.p. LD_{50} for rat was 1,200 mg di(2-ethylhexyl) phosphate/kg bw. Di(2-ethylhexyl) phosphate exhibit strong corrosive effect in cornea at 5 µl doses (1% solution) as well as skin irritating effects. No mutagenic activity was observed. All endpoints have not been sufficiently investigated. Dermal toxicity and local corrosive effects on skin and eyes seems to be the most severe effects. Sufficient data are not available for classification. DEHPA has been classified by Bayer AG in 1993 as C (*Corrosive*); R34 (*Causes burns*) and Xn (*Harmful*); R21 (*Harmful in contact with skin.*
	No data found to determine reproductive toxicity or teratogenicity.
Environment	Conflicting data on the biodegradability of di(2-ethylhexyl) phosphate are available. The compound is here evaluated as inherently biodegradable. The BCF values indicates that di(2-ethylhexyl) phosphate does not bioaccumulate. The available ecotoxicological data indicates that di(2-ethylhexyl) phosphate is harmful algae, crustaceans and fish.

References

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http://toxnet.nlm.nih.gov

5 CCRIS - Chemical Carcinogenesis Research Information System
http://toxnet.nlm.nih.gov

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http://ntp-server.niehs.nih.gov

7 Genetox - Genetic Toxicology
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Tri(2-ethylhexyl) phosphate

CAS number: 78-42-2

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

Tri(2-ethylhexyl) phosphate (TEHPA) is a slightly flammable compound when exposed to heat. It has a low water solubility and vapour pressure. THEPA has a high fat solubility

Emission

No data found

Exposure

TEHPA has been found fresh water, in seawater and in sewage treatment plant influents, effluents and sludge.
TEHPA has also been found in several types of food and in drinking water.

Health

Tri(2-ethylhexyl) phosphate appears to have only slight acute oral toxicity. LD_{50} in rats was more than 37.08 g/kg and LD_{50} was approx. 46.0 g/kg in rabbits. In connection with inhalation the toxicity expressed as LC_{50} were 450 mg/m^3/30 minutes. Tri(2-ethylhexyl) phosphate produces moderate erythema in skin irritation test and slight irritation to eyes at doses from 0.01 ml to 0.05 ml. No sufficient data were found on skin sensitisation.

In subchronic and chronic toxicity tests NOEL for TEHPA in mouse was less than 500 mg/kg bw, NOEL for male rats was 100 mg/kg and NOEL for rats was 430 mg/kg. In an inhalation test 10.8 mg/m3 produced high mortality. Dose related effects on trained behaviour were observed.

TEHPA was not mutagenic and was not found genotoxic in chromosome aberration test and micronuclei assays. Slight evidence of carcinogenicity was observed in mouse, but it has been concluded that the substance is not likely to cause cancer in humans. No data were found on reprotoxicity, embryo toxicity and teratogenicity. Slight neurotoxic effects were observed in dogs.

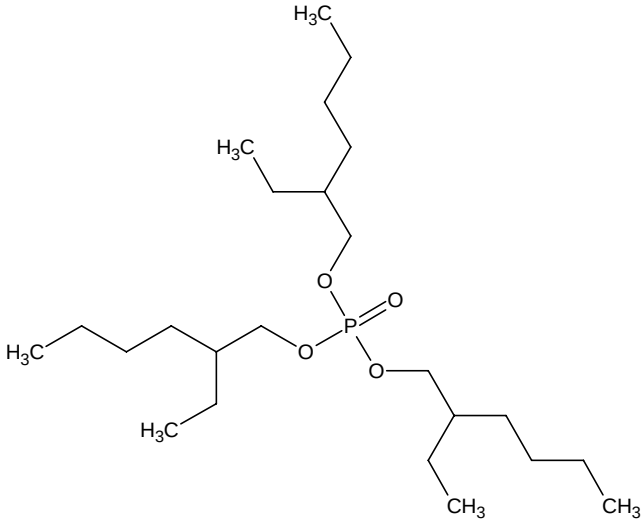
Based on the available data the critical effect appears to be repeated dose toxicity after oral administration and local effects. Bayer AG has classified TEHPA according to the substance directive in 1993 as follows: Xi (*Irritant);* R36/38 *(Irritating to skin and eyes).*

Environment

The available data on biodegradation do not indicate that TEHPA biodegrades readily.
The only measured BCF value indicates that TEHPA does not bioaccumulate. It should be noted that the measured Log P_{ow} indicates a potential for bioaccumulation.
The available ecotoxicological data indicate, that tri(2-ethylhexyl) phosphate is harmful to algae. The available data on crustaceans are insufficient to make a classification. A low range result (10 mg/l) exists from a ciliate test.

Tri(2-ethylhexyl) phosphate

Identification of the substance

CAS No.	78-42-2	
EINECS No.	201-116-6	
EINECS Name	Tris(2-ethylhexyl) phosphate	
Synonyms	Trioctyl phosphate, phosphoric acid tris(2-ethylhexyl) ester, 2-ethylhexanol phosphate triester, 2-ethyl-1-hexanol phosphate, triethylhexyl phosphate, TOF, Disflamoll TOF, Flexol TOF, Kronitex TOF, NCI-C54751, TOF, tris(2-ethylhexyl) phosphate.	
Molecular Formula	$C_{24}H_{51}O_4P$	
Structural Formula		
Major Uses	Flame retardant plasticiser for polyvinyl chloride resins.	[3]
	Solvent, anti foaming agent and plasticiser. Colour carrier in polymer colouring. Viscosity increaser.	[3]
IUCLID	The compound is not included in the IUCLID HPVC list.	
EU classification	The compound is not included in Annex I to 67/548/EEC	[10]

Physico-chemical Characteristics

Physical Form	Viscous colourless liquid	[3,15]

Tri(2-ethylhexyl) phosphate

Molecular Weight (g/mole)	434.72	
Melting Point/range (°C)	-74 <70 -70 to –90	[3] [15] [10]
Boiling Point/range (°C)	220 at 5 mm Hg 210-220 at 37.5-49.5 mm Hg 210 at 14.8 mm Hg	[3] [10] [15]
Decomposition Temperature (°C)	No data found	
Vapour Pressure (mm Hg at °C)	0.23 at 150 °C 1.9 at 200 °C ♦8.3×10^{-7} at 25 °C 1.4×10^{-4} at 25 °C	[3] [6] [10] [15]
Density (g/cm^3 at °C)	0.92 (unknown temperature) 0.92-0.926 (unknown temperature) 0,92 at 20 °C	[6] [10] [15]
Vapour Density (air=1)	No data	
Henry's Law constant ($atm/m^3/mol$ at °C)	0.008 (estimated, unknown temperature)	[10]
Solubility (g/l water at °C)	<0.1 at 20 °C <0.001 at 18 °C < 0.0005 at 20 °C ♦0.0006 at 24 °C	[3] [6] [10] [10]
Partition Coefficient (log P_{ow})	4.23 0.8-4.22 4.22 ♦4.1-5.04 5,04	[8] [12] [16] [10] [15]
pK_a	♦1.72 (estimated) at 25 °C ♦2.12 (estimated)	[10] [10]
Flammability	Slightly flammable when exposed to heat or flame.	[3]
Explosivity	No data found	
Oxidising Properties	No data found	
Migration potential in polymer	No data found	

Emission Data

Tri(2-ethylhexyl) phosphate

During production	No data found	

Exposure Data

Aquatic environment, incl. sediment	Estuary 1-5 ng/l Rw 20-290 ng/l Sediment 2-70 µg/kg Dw 0.3 ng/l Fw (maximum measurements) 40-120 ng/l	[10] [10] [10] [10] [10]
Terrestrial environment	No data found	
Sewage treatment plant	Influent: 7-144 ng/l Effluent: 0.5 ng/l	 [10] [10]
Working environment	Indoor, office 5-6 ng/m^3	[10]
Consumer goods	No data found	
Man exposed from environment	No data found	
”Secondary poisoning”	Oil and grease (food for children) 38.5 µg/kg Meat, oil and greases 6.7 µg/kg	[10] [10]
Atmosphere	No data found	
Dermal	No data found	

Toxicological data

Observations in humans	♦A 24 hours exposure of the underarm on six test persons did not result in any irritation of the skin.	[10]

Acute toxicity

Oral	Tri(2-ethylhexyl)phosphate appears to have only slight acute oral toxicity. Mouse ♦LD_{50}> 12,800 mg/kg bw	[3] [3]

	Rat: No specific doses and duration specified. LD_{50}= 37 g/kg. ♦ LD_{50}> 2,000 mg/kg bw ♦ LD_{50}= 37,080 mg/kg bw ♦ LD_{50}= 39,800 mg/kg bw 18,400 and 36,800 mg/kg bw. Mortality in animals dosed 18,400 mg/kg bw where 1 of 6 animals died and in dose group 36,800 mg/kg bw where 2 of 6 animals died. LD_{50}>9,200 mg/kg bw (> 10 ml/kg bw)	[10] [10] [10, 17] [10] [6,10] [10]
	Rabbit: No doses specified, gavage. LD_{50} approx. 46.0 g/kg. No specific doses and duration specified. LD_{50}= 46 g/kg. ♦ LD_{50}= 46,000 mg/kg bw	[3] [6] [10]
Dermal	Rabbit: No specific doses and duration specified. LD_{50}= 20 g/kg. ♦ LD_{50}= 18,400 mg/kg bw	[6] [10]
Inhalation	Rat ♦ 450 mg/m^3. No mortality was observed.	[10]
	Rat and rabbit: Dose and duration not specified. No toxic effects were observed.	[3]
	Guinea pig: ♦ No specific doses and duration specified. LD_{50}= 450 mg/m^3/30 minutes. 448 mg/m^3 (1,5 h), average particle size=1.5µm. 6 of 10 animals died.	[6,10] [10]
Other routes	Mouse LD_{50}= 7,200 mg/kg bw, route unknown.	[10]
	Rat and rabbit: Dose and duration not specified, intravenously. No toxic effects were observed. Dose and duration not specified, intratracheally. No toxic effects were observed.	[3] [3]
	Rabbit 358 mg/kg bw. 2 of 6 animals died. 1,811 mg/kg bw. 1 of 6 animals died in the dose range from 690 to 1,811 mg/kg bw.	[10] [10]

Skin irritation	Rat and rabbit Single application of TEHPA resulted in hyperglycemia, reduced growth of hair, hair loss and dryness of the skin.	[10]
	Rabbit ♦250 mg (24 h) applied to shaved skin. Moderate erythema was observed within 24 h and lasted one week.	[3,10]
	No dose specified (24 h), occlusive application in ear. Swelling and redness of skin.	[10]
	♦10-20 ml, single application on skin on the back of young rabbits. Mortality was observed after single application of test substance.	[10]
	No evidence of systematic intoxication.	[10]
Eye irritation	Rabbit No dose specified (24 h). Rated one on a numerical scale from 1 to 10 according to degree of injury. Particular attention to condition of cornea. Most severe injury observed was rated 10.	[3]
	♦0.1-0.5 ml (24 h), young animals tested. Moderate conjunctivitis that cleared up after 24 h.	[3,10]
	♦0.01-0.05 ml application in eye of young animals. Light irritation was observed.	[10]
	Dose not specified, young animals tested. Flood of tears, darkening of the cornea and hair loss in the eye surroundings.	[10]
	No evidence of systematic intoxication.	[3]
Irritation of respiratory tract	No data found.	
Skin sensitisation	Guinea pig ♦Not sensitising.	[10]

Subchronic and Chronic Toxicity

Oral	Of low toxicity to mice and rat	[10]

	Mouse: Up to 3,000 mg/kg bw (14 d) oral probe. No toxic effects were observed.	[10]
	♦*B6C3F1* mice*:* 0, 500, 1,000, 2,000, 4,000, 8,000 mg/kg bw/d (13 w, 5 d/w) oral probe. NOEL<500 mg/kg bw. Gastritis was dose dependent and lowest dose observation was in the 500 mg/kg bw group and isolated incidences of ulceration was observed in dose groups from 2,000 mg/kg bw group. Decrease in bw was observed in the female 4,000 mg/kg bw dose group and in the male 8,000 mg/kg bw.	[10]
	B6C3F1 mice*:* 0, 375, 750, 1,500, 3,000, 6,000 mg/kg bw/d (14 d) 5 animals/sex/dose group, oral probe. NOEL = 3,000 mg/kg bw. Decrease in bw in 6,000 mg/kg bw males and in 3,000 mg/kg bw females. Decreased activity and raw throat.	[10]
	Rat: *Fisher 344* rats: 0, 375, 750, 1,500, 3,000, 6,000 mg/kg bw/d (14 d) 5 animals/sex/dose group, oral probe. NOEL, males =750 mg/kg bw. Decrease in bw in 1,500 mg/kg bw males and in 3,000 mg/kg bw females after 14 d.	[10]
	♦*(Crj: CD(SD))* rats: 30, 100, 300, 1,000 mg/kg bw/d (28 d, thereafter 14 d observation) 6 animals/sex/dose group, oral probe. NOEL=100 mg/kg bw. 300 mg/kg bw females had decreased prothrombin time and decreased partial thromboplastin time in 1,000 males. Decrease in serum choline esterase activity in male 300 mg/kg.	[3,10]
	♦*Sherman* rats: 110-1,550 mg/kg bw/d (30 d) 5 animals/sex/dose group. NOEL 430 mg/kg bw. Decrease in bw in the 1,550 dose groups (LOEL). 0, 250, 500, 1,000, 2,000, 4,000 mg/kg bw/d (13 w) 10 animals/sex/dose group, oral probe. NOEL, female =1,000 mg/kg bw. Decrease in growth was observed in the female 2,000 mg/kg bw dose group and in the male 4,000 mg/kg bw after 13 w.	[10]
Inhalation	Rat: 0.23, 0.63 mg/m^3 (16 w, 4 h/d) 30 females. Dose group 0.23 mg/m^3 showed decrease in choline esterase activity in blood. Decrease in Beta-globuline in serum. Dose group 0.63 mg/m^3 showed change in content of hippurie acid in the leucocyte number. The study does not comply with OECD study criteria.	[10]

	Guinea pig: *Hartley:* 1.6, 9.6 mg/m^3 (12 w, 5 d/w, 6 h/d), 20 males, average particle size = 3.8 µm. Decrease in kidney weight. Increased bw in 9.6 mg/m^3. Several histopathological changes. Several other observations but the study does not comply with modern study criteria.	[10]
	♦10.8, 26.4, 85 mg/m^3 (12 w, 5 d/w, 6 h/d), 10 animals/dose group, average particle size = 4.4 µm. High mortality in all dose groups due to lung infections. Increase in relative lung and kidney weights in the highest dose groups.	[10]
	Dog: ♦10.8, 26.4, 85 mg/m^3 (12 w, 5 d/w, 6 h/d), 1 animal/sex/dose group, average particle size = 4.4 µm. Minor chronic infection in lungs. Slight behavioural changes.	[10]
	Monkey: ♦*Rhesus:* 10.8, 26.4, 85 mg/m^3 (12 w, 5 d/w, 6 h/d), 1 animal/sex/dose group, average particle size = 4.4 µm. No effects were observed.	[10]
Dermal	Rabbit: ♦92 mg/animals/d (5 d/w, observation period after treatment: 3-17 d) 10 and 20 applications. Hyperkeratose, mild parakeratose, acute dermatitis and mild thickening of the epidermis. The effects disappeared 17 days after the 10th application. No systemic changes.	[10]
Other routes	Chicken: Doses not specified, route and duration unspecified. No demyelinating action found. Positive control: Tri-ortho-cresyl phosphate.	[3]
	Doses not specified, route and duration not specified. No neuropathological or inhibition of cholineesterase.	[3]
	Cat: 920 mg/kg bw/d (1 ml/kg bw)(4 w, 5 d/w), 2 cats. No decrease in the cholineesterase activity in the erythrocytes.	[10]
	Dog: ♦Doses not specified, route and duration unspecified. Dose related effect on trained behaviour of dogs.	[3]
	Monkey: Doses not specified, route and duration unspecified. No effect on trained behaviour of monkeys.	[3]

Tri(2-ethylhexyl) phosphate

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	*Salmonella typhimurium*:	
	No dose specified, strain indicators: TA98, TA100, TA1535, TA1537. Not mutagenic. All strains tested both with and without metabolic activation.	[3,5]
	100-10,000 µg/plate, strain: TA98, TA100, TA1535, TA1537. Not mutagenic. All strains tested both with and without metabolic activation.	[10]
	♦20-12,500 µg/plate, strain: TA98, TA100, TA1535, TA1537. Not mutagenic. All strains tested both with and without metabolic activation.	[10]
	100-10,000 µg/plate, strain: TA98, TA100, TA1535, TA1537. Not mutagenic. All strains tested both with and without metabolic activation.	[10]
	312.5-5,000 µg/plate, strain: TA98, TA100, TA1535, TA1537. Not mutagenic. All strains tested both with and without metabolic activation.	[10]
	Escherichia coli:	
	312.5-5,000 µg/plate. Not mutagenic. All strains tested both with and without metabolic activation.	[10]
	Mouse lymphoma:	
	♦Up to 74.1 µl/ml. All strains tested both with and without metabolic activation. No metabolic activation.	[10]
	Drosophila melanogaster:	
	♦50,000 ppm in a sugar solution (3 d). No sex-linked recessive lethal mutations.	[10]
	50,000 ppm in 0.7% NaCl, injection. No sex-linked recessive lethal mutations.	[10]
Gene Mutation	No data found	
Chromosome Abnormalities	CHO:	
	♦Up to 1670 µg/ml. No chromosome aberration.	[10]
	Up to 839 µg/ml. No sister chromatide exchange.	[10]
	CHL:	
	3 -11 µg/ml. No chromosome aberration. No metabolic activation system.	[10]
	1,100 -4,400 µg/ml. No chromosome abbreviation. No metabolic activation system.	[10]

Other Genotoxic Effects	Mouse: 0, 500, 1,000, 1,500, 2,000, 3,000 mg/kg bw (3 d) daily i.p. No micronuklei observed.	[10]
	Rat: ♦0, 0.25, 0.50 mg/lair (2 w, 5 d/w, 6 h/d) altogether 9 exposures. No micronuclei observed.	[10]
	Chicken: Doses not specified. No demyelinating action found. Positive control: Tri-ortho-cresyl phosphate. Doses not specified. No neuropathological or inhibition of cholineesterase.	[3] [3]
Carcinogenicity	Mouse: *B6C3F1* mice*:* 500 and 1,000 mg/kg bw; (103 w, 5 d/w), 50 animal/dose group, in corn oil by gavage. Increased incidence of folicular cell hyperplasia of the thyroid. In females significant increase of hepatocellular carcinomas in the high dose group. Decrease in hemangiosarcomas of the circulatory system in males and hematopoietic system in females. Some incidence of carcinogenicity in the 1,000 mg/kg female group. No evidence of carcinogenicity in males. ♦*B6C3F1* ♀ mice 0, 500 and 1,000 mg/kg bw (102-104 w) females, in corn oil by gavage, 5 d/w. Carcinoma and adenoma in liver. Evidence of carcinogenicity.	[3,5,6,10] [5]
	Rat: ♦*Fisher 344* rats: 2,000, 4,000 mg/kg bw male; 1,000, 2,000 mg/kg bw female; (103 w, 5 d/w), 50 animals/dose group, in corn oil by gavage. Results - male: Bw gain was depressed. Dose related increase in pheochromocytoma of adrenal glands. 2 malignant pheochromocytoma in the high dose group. High increase compared to control, but incidence in this group unusually low. Decreased incidence of acinar cell adomas of the pancreas. Evidence of carcinogenicity was equivocal in dose group 2,000 and 4,000 mg/kg. Results - female: Decreased incidence of fibroadenomas of mammary glands in low dose groups. No evidence of carcinogenicity in female rats. 0, 2,000, 4,000 mg/kg bw (102-104 w), males, in corn oil by gavage, 5 d/w. Results: Equivocal evidence of carcinogenicity. 0, 1,000, 2,000 mg/kg bw (102-104 w), males, in corn oil by gavage, 5 d/w. Results: No evidence of carcinogenicity.	[3,5,6,10] [5] [5]

	Human: Based on the slight carcinogenicity and no mutagenicity and genotoxicity, TEPH is evaluated as unlikely to be carcinogenic to humans by an ECETOC working group.	[10]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	No data found.	
Teratogenicity	No data found.	
Other Toxicity Studies	No data found.	

Neurotoxicity and Toxicokinetics

Neurotoxicity	Chicken: 500, 2,500 mg/kg bw, 8 animals. Result: One animal of 8 died in the high dose group. 250, 500, 2,500 mg/kg bw. Result: No observed effects.	[10] [10]
	Dog and monkey: ♦ 10.8, 26.4, 85 mg/m^3 (12 w, 6 h/d, 5 d/w) 2 animals/dose group. Result: Dog - Decreased results of the multiple stimuli conditioned avoidance test. Monkey - no effects were observed in the ability of visual discrimination.	[10]
Toxicokinetics	Rat: ♦ TEHPA metabolised to at least one other compound.	[3]
Other effects	HeLa cell: 144 and 320 mg/ml. Result: No effects observed in the low dose group. TEHPA precipitated at 320 mg/ml. Metabolic inhibition test.	

Ecotoxicity Data

Algae	*Chlorella emersonii:* ♦ EC_{50}(48h) =50-100 mg/l	[10]
Crustacean	*Culex tarsalis:* LC_{50}(24h)>1 mg/l	[10]
	Daphnia magna: EC_{50}(48h)>0,08 mg/l	[15]

Tri(2-ethylhexyl) phosphate

Fish	*Brachydanio rerio* (fw): LC_0(96h) >100 mg/l	[12,15]
Bacteria	Activated sludge: EC_{50}(3h)>100 mg/l	[15]
Terrestrial organisms	No data found.	
Other toxicity information	*Tetrahymena pyriformis:* ♦EC_{50}(24h) =10 mg/l	[18]

Environmental Fate

BCF	251 (estimated)	[10]
	251-3,837 (estimated)	[10]
	♦2.4-22 Cyprius carpio, MITI	[19]
	2-22 (42h)	[15]
Aerobic biodegradation	Aquatic – ready biodegradability tests:	
	♦0 % at 100 mg/l, in 28 d, OECD 301C	[19]
	♦0 % at 4.76 mg/l, in 28 d, OECD 301D	[19]
	Aquatic – other tests:	
	40-60 % in 2 d, activated sludge	[9]
	20 % in 1 d, activated sludge	[9]
	20 % in 1 d, adapted activated sludge	[9]
	0-90 % at 3.22 mg/l, in 30 d, RDA	[9,10]
	0 % in 28 d, waste water	[9]
	55 % in 2 d, activated sludge	[12]
	60 % in 2 d, adapted activated sludge	[12]
	20 % at 2 mg/l/24h, in 238 d, SCAS	[10,12]
	0 % at 100 mg/l in 28 d, SCAS	[10,12]
	0 % at 8 mg/kg in 7 d, mesophile sludge stabilisation	[10]
	20.4-35.9 % at 1-20 mg/l in 7 d, river water	
	20.0-42.2 % at 1-20 mg/l in 14 d, river water	[10]
	65.5 % at 1-20 mg/l in 15 d, river water	[10]
	9.9 % at 1 mg/l in 7 d, sea water	[10]
	1.2 % at 1 mg/l in 8 d, sea water	[10]
	32.5-73.2 % at 1 mg/l in 14 d, sea water	[10]
	12-28 % at 3-13 mg/l/24h, in 34 d, SCAS	[10] [16]
Anaerobic biodegradation	25 % at 1.4 mg/l in 70 d, mesophile sludge stabilisation.	[10]
Metabolic pathway	No data found.	
Mobility	No data found.	

Tri(2-ethylhexyl) phosphate

Conclusion

Physical-chemical	Tri(2-ethylhexyl) phosphate (TEHPA) is a slightly flammable compound when exposed to heat. It has a low water solubility and vapour pressure. THEPA has a high fat solubility
Emission	No data found.
Exposure	TEHPA has been found fresh water, in seawater and in sewage treatment plant influents, effluents and sludge. TEHPA has also been found in several types of food and in drinking water.
Health	Tri(2-ethylhexyl) phosphate appears to have only slight acute oral toxicity. LD_{50} was more than 37 g/kg in rats and approx. 46 g/kg in rabbits. In connection with inhalation the toxicity expressed as LD_{50} were 450 mg/m^3/30 minuttes. Tri(2-ethylhexyl) phosphate produces moderate erythema in skin irritation test and slight irritation to eyes at doses from 0.01 ml to 0.05 ml. No sufficient data were found on skin sensitisation. In subchronic and chronic toxicity tests NOEL for TEHPA in mouse was less than 500 mg/kg bw, NOEL for male rats was 100 mg/kg and NOEL for rats was 430 mg/kg. In an inhalation test 10.8 mg/m^3 produced high mortality. Dose related effects on trained behaviour were observed. TEHPA was not mutagenic and was not found genotoxic in chromosome aberration test and micronuclei assays. Slight evidence of carcinogenicity was observed in mouse. No data were found on reprotoxicity, embryo toxicity and teratogenicity. Slight neurotixic effects were observed in dogs. Based on the slight carcinogenicity and no mutagenicity and genotoxicity, TEPHA is evaluated as unlikely to be carcinogenic to humans by an ECOTOC working group. Based on the available data the critical effect appears to be repeated dose toxicity after oral administration and local effects. TEHPA has been classified according to the substance directive by Bayer AG in 1993 as follows: Xi (*Irritant);* R36/38 *(Irritating to skin and eyes).*

Environment	The available data on biodegradation do not indicate that TEHPA biodegrades readily. The only measured BCF value indicates that TEHPA does not bioaccumulate. It should be noted that the measured Log P_{ow} indicates a potential for bioaccumulation. The available ecotoxicological data indicate, that tri(2-ethylhexyl) phosphate is harmful to algae. The available data on crustaceans are insufficient to make a classification. A low range result (10 mg/l) exists from a ciliate test.

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Tri-2-ethylhexyl trimellitate

CAS number: 3319-31-1

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

Tri-2-ethylhexyl trimellitate is a compound with low water solubility and, low vapour pressure a high fat solubility. Migration from PVC to sunflower oil, isooctane or ethanol was 1,280; 1,220 and 450 mg/dm2 respectively, which is relatively high.

Emission

No data found

Exposure

No data found

Health

Sufficient data were not found for a profound assessment but data indicate that the substance is moderately irritating towards skin, eyes and respiratory tract and harmful by inhalation.

Concerning sensitisation animal experiments indicate that it does not induce sensitisation in Guinea-pigs. Data on mutagenicity indicate that tri-2-ethylhexyl trimellitate is not mutagenic to S*almonella typhimurium.*

The identified critical effect is related to systemic effects from inhalation of the substance. Based on the available information tri-2-ethylhexyl trimellitate should be classified Xn *(Harmful)*; R20 *(dangerous by inhalation)*.

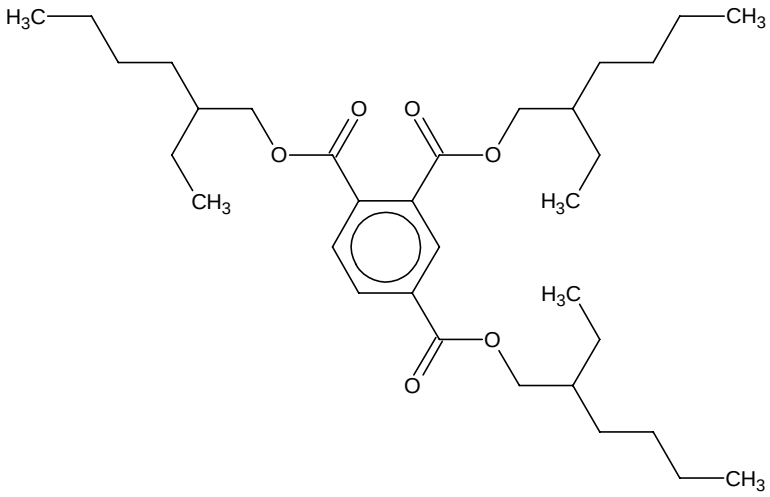
Environment

The available data indicate that tri-2-ethylhexyl trimellitate does not biodegrade readily or inherently.
The only available measured Log P_{ow} value, indicates that tri-2-ethylhexyl trimellitate bioaccumulates.
The available acute 50 % effect concentrations are all given as ranges, and it therefore not possible to evaluate the acute ecotoxicity of tri-2-ethylhexyl trimellitate. A NOEC based on chronic data for crustaceans was

0.082 mg/l.

Tri-2-ethylhexyl trimellitate

Identification of the substance

CAS No.	3319-31-1
EINECS No.	222-020-0
EINECS Name	Tris(2-ethylhexyl) benzene-1,2,4-tricarboxylate
Synonyms	Tris(2-ethylhexyl) trimellitate, trioctyl, trimellitate tris(2-ethylhexyl) ester, Kodaflex TOTM, tri(2-ethylhexyl)trimellitate ester, 2-ethylhexyl trimellitate, tris(2-ethylhexyl)benzenetricarboxylate, Bisoflex TOT, tri-2-ethylhexyl trimellitate.
Molecular Formula	$C_{33}H_{54}O_6$
Structural Formula	
Major Uses	No data found
IUCLID	The substance is included in the IUCLID HPVC list.
EU classification	The compound is not included in Annex I to 67/548/EEC

Physico-chemical Characteristics

Physical Form	Yellow oily liquid	[6]
Molecular Weight (g/mole)	546.79	
Melting Point/range (°C)	-35 – -30 °C	[1a]
Boiling Point/range (°C)	414	[15]

Tri-2-ethylhexyl trimellitate

Decomposition Temperature (°C)	No data found	
Vapour Pressure (mm Hg at °C)	♦5.5×10^{-5} at 20 °C 3.94×10^{-11}	[1a] [15]
Density (g/cm^3 at °C)	0.985-0.992 at 20 °C 0.989 (unknown temperature)	[1a] [2]
Vapour Density (air=1)	No data found	
Henry's Law constant ($atm/m^3/mol$ at °C)	4.45×10^{-7} (estimated, unknown temperature)	[8,15]
Solubility (g/l water at °C)	<1 mg/l at 20 °C ♦0.00039 mg/l at 25 °C 0.1 mg/l at 25 °C	[1a,6] [1a] [15]
Partition Coefficient (log P_{ow})	♦4.35 at 25 °C 12.41 (estimated) 11.59 (estimated)	[1a] [8] [15]
pK_a	No data found	
Flammability	No data found	
Explosivity	No data found	
Oxidising Properties	No data found	
Migration potential in polymer	♦ Migration from PVC to sunflower oil, isooctane or ethanol was 1,280; 1,220 and 450 mg/dm^2 respectively in studies over 1-3 days at the same, corresponding to 30-80% of the total TETM amount in the PVC piece.	

Emission Data

During production	No data found

Exposure Data

Aquatic environment, incl. sediment	No data found
Terrestrial environment	No data found
Sewage treatment plant	No data found
Working environment	No data found

Tri-2-ethylhexyl trimellitate

Consumer goods	No data found
Man exposed from environment	No data found
”Secondary poisoning”	No data found
Atmosphere	No data found
Dermal	No data found

Toxicological data

Observations in humans	Mist and fumes from hot processing may cause irritation to eyes, nose throat and upper respiratory tract, nausea and vomiting. Significant absorption through the skin is unlikely.	[1a, 17]

Acute toxicity

Oral	Rat	
	♦ LD_{50} rat >3.2 g/kg bw.	[1, 17]
	♦ LD_{50} rat = 9850 mg/kg bw	[1a]
	Mouse	
	♦ LD_{50} mouse > 3.2 g/kg bw.	[1a, 17]
Dermal	Rabbit	
	LD_{50} (24 hour covered) >1.98 g/kg bw	[17]
	♦ LD_{50} (OECD 402/1981) > 1.97 g/kg bw	[1a]
Inhalation	Rat:	
	♦ LC_{50} = 2.6 mg/l (4 hours)	[1a]
	♦ Moderate irritation resulted from a 6 hours exposure to 16 ppm (probably in rats) but a concentration on 2640 mg/m^3 in 6 hours exposure caused severe irritation (probably the respiratory tract) and death. No death occurred at a concentration equal to 230 mg/m^3.	[17]
Other routes	Rat	
	i♦.p LD_{50} > 3200 mg/l	[1a]
	Mouse	
	i.p LD_{50} > 3200 mg/l	[1a]

Skin irritation	Rabbit ♦0.5 ml neat substance (occlusive, 4 hours). Slightly irritating, not classifiable. (OECD 404/1984) 0.5 ml neat substance (occlusive 24 hours). Slightly irritating, not classifiable. (FHSAR - 16FSR) Guinea pig 0.5 ml neat substance (occlusive, 24 hours). Slightly irritating. 0.5 ml neat substance (occlusive, 24 hours). Not irritating. (Buehler)	[1a] [1a] [1a] [1a]
Eye irritation	Rabbit ♦0.1 ml. Slightly irritating, not classifiable. (OECD 405/1984) 0.1 ml neat substance. Slightly irritating, not classifiable. (FHSAR - 16FSR)	[1a] [1a]
Irritation of respiratory tract	Rats exposed to an estimated concentration of 230 mg/m^3 for 6 hr. showed minimal irritation. See also "Inhalation"	[17]
Skin sensitisation	Guinea pig ♦0.5 ml neat substance (occlusive, 24 hours, 10 applications). Challenge after 2 weeks. Not sensitising. (OECD 406/1981)	[1a, 17]

Subchronic and Chronic Toxicity

Oral	Rat ♦*Fisher 344:* 0, 0.2% (184 mg/kg bw/d), 0.67% (650 mg/kg bw/d) and 2% (1826 mg/kg bw/d) in diet for 28 days. LOAEL = 184 mg/kg bw. Slightly increased liver weights and liver enzymes, decreased erythrocytes, increased leucocytes, and raised cholesterole levels at 0.67%. Increased palmitoyl CoA at 0.2%. Slight peroxisome proliferation at 2%. *Fisher 344:* 0, 200 mg/kg bw/d, 700 mg/kg bw/d and 2000 mg/kg bw/d per gavage for 21 days. LOAEL = 200 mg/kg bw. Slight increase in hepatic peroxisomes in males at top dose level. Increased enzyme activity in males and females at 200 and 2000 mg/kg bw. *Fisher 344:* 0 and 1000 mg/kg bw/d per gavage for 28 days. LOAEL = 1000 mg/kg bw. Non-significant liver effects.	[1a] [1a] [1a]

	(Albino rats) 0 and 985 mg/kg bw/d injections for 7 days. No effects. NOAEL = 985 mg/kg bw.	[1a]
	Mouse 14 and 42 mg/kg bw/d injections for 14 days. Increased relative spleen and liver weights in top dose group. LOAEL = 42 mg/kg bw. (Limited data)	[1a]
	Dog ♦14 and 42 mg/kg bw/d injections for 14 days. Increased relative spleen and liver weights in top dose group. LOAEL = 42 mg/kg bw. (Limited data)	[1a]
Inhalation	No relevant data found.	
Dermal	No relevant data found.	

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	*Salmonella typhimurium*: ♦0, 100, 333, 1000, 3333, 10000 µg/plate. Test strain: TA100, TA1535, TA97 or TA 98. No mutagenicity was observed. Ames, pre-incubation, test with and without metabolic activation.	[1a]
	Neat urine from male Sprague-Dawley rats gavaged daily for 15 days with 2 g/kg bw. Test strain: TA97, TA98, TA 100 or TA1535. No mutagenicity was observed. Ames with and without metabolic activation.	[1a]
	Chinese hamster ovary cells: ♦5 - 200 nl/ml (6 concentrations). Unschedules DNA synthesis without metabolic activation. No mutagenicity observed.	[1a]
	Primary rat hepatocytes: ♦250 - 5000 nl/ml. HGPRT assay with and without metabolic activation. No indication of UDS observed.	[1a]
	A dose of approximately 1400 mg/kg bw was not mutagenic in a dominant lethal test in mice.	[1a, 17]
Chromosome Abnormalities	No relevant data found.	
Other Genotoxic Effects	No relevant data found.	
Carcinogenicity	Mouse (strain A): ♦Approx. 1400 mg/kg bw (possibly per day). Tests in mouse with a propensity to form pulmonary adenoms were negative. No further details.	[1a]

Tri-2-ethylhexyl trimellitate

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	No relevant data found.	
Teratogenicity	No relevant data found.	
Other Toxicity Studies	No relevant data found.	

Toxicokinetics

Toxicokinetics	Metabolic studies in rats have shown that following the administration of 100 mg/kg bw by stomach tube , about 64% was excreted unchanged in the faeces, 11% and 16% were excreted as metabolites in the faeces and urine respectively, and less than 0.6% remained in the tissues after 6 days.	[1a, 17]
	Is the substance given intravenously, it will mainly accumulate in the liver (72%), lungs and spleen.	[1a]

Ecotoxicity Data

Algae	No data found.	
Crustacean	*Daphnia magna* (fw): EC_{50}(48h)>1 mg/l ♦NOEC(21d)<= 0.082 mg/l	 [1a] [1a]
Fish	*Salmo gairdneri* (fw): LC_{50}(96h)>1 mg/l	 [1a]
Bacteria	No data found.	
Terrestrial organisms	No data found.	
Other toxicity information	No data found.	

Environmental Fate

BCF	No data found.	

Tri-2-ethylhexyl trimellitate

Aerobic biodegradation	Aquatic – ready biodegradability tests: ♦ 14 % at 100 mg/l in 28 d, OECD 301 C	[1a]
	Aquatic – other tests: 4.2 % at 30 mg/l in 28 d, OECD 301C or 302C	[16]
Anaerobic biodegradation	No data found.	
Metabolic pathway	No data found.	
Mobility	No data found.	

Conclusion

Physical-chemical	Tri-2-ethylhexyl trimellitate is a compound with low water solubility and, low vapour pressure a high fat solubility. Migration from PVC to sunflower oil, isooctane or ethanol was 1,280; 1,220 and 450 mg/dm^2 respectively, which is relatively high.
Emission	No data found.
Exposure	No data found.
Health	Not sufficient data. Data on mutagenicity indicate that tri-2-ethylhexyl trimellitate is not mutagenic to S*almonella typhimurium.* The identified critical effect is related to systemic effects from inhalation of the substance. Based on the available information TETM should be classified Xn *(Harmful)*; R20 *(dangerous by inhalation)*.
Environment	The available data indicate that tri-2-ethylhexyl trimellitate does not biodegrade readily or inherently. The only available measured Log P_{ow} value, indicates that tri-2-ethylhexyl trimellitate bioaccumulates. The available acute 50 % effect concentrations are all given as ranges, and it therefore not possible to evaluate the acute ecotoxicity of tri-2-ethylhexyl trimellitate. A NOEC based on chronic data for crustaceans was 0.082 mg/l.

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http://toxnet.nlm.nih.gov

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o-Toluene sulphonamide

CAS number: 88-19-7

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

o-Toluene sulphonamide is a compound with a low water solubility, moderate fat solubility and a low vapour pressure.

Emission

No data found

Exposure

No data found

Health

No data found on acute toxicity, subchronic and chronic toxicity.
o-Toluene sulphonamide is reported as teratogenic in rats, but no detailed descriptions of the study design is available. Only weak mutagenic activity is shown.
There is limited evidence that OTSA is carcinogenic when administered orally to rats. This has been suggested as the cause of carcinogenicity of saccharin. The available data suggest that OTSA impurities at the levels normally found in commercial saccharin do not contribute to the carcinogenicity of saccharin.

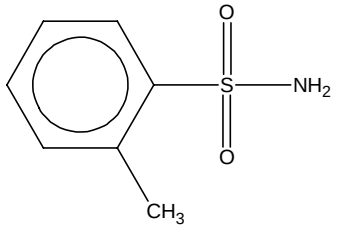
Based on very limited data the critical effect has been identified as possible teratogenicity.
It is not possible to evaluate the data against the classification criteria for teratogenicity, as information is too sparse. Other described effects are not classifiable.

Environment

The available data on biodegradation indicate that o-toluene sulphonamide does not biodegrade readily.
The available BCF values indicate that o-toluene sulphonamide do not bioaccumulates.

o-Toluene sulfonamide

Identification of the substance

CAS No.	88-19-7	
EINECS No.	201-808-8	
EINECS Name	Toluene-2-sulphonamide	
Synonyms	2-methyl-benzenesulphonamide, o-methylbenzenesulphonamide, 2-methylbenzensulphonamide, toluene-2-sulphonamide, o-toluene sulfonamide.	
Molecular Formula	$C_7H_9NO_2S$	
Structural Formula		
Major Uses	Plasticiser in the saccharin and amino resins production.	[3]
	Reactive plasticiser.	[3]
	Plasticiser for hot-melt adhesives.	[3]
	Fluorecent pigment.	[3]
IUCLID	The substance is not included in the IUCLID HPVC list.	
EU classification	The compound is not included in Annex I to 67/548/EEC	

Physico-chemical Characteristics

Physical Form	Colourless octahedral crystals.	[3]
Molecular Weight (g/mole)	171.23	
Melting Point/range (°C)	156.3	
Boiling Point/range (°C)	214 °C at 997.5 mm Hg	[3]
Decomposition Temperature (°C)	No data found	
Vapour Pressure (mm Hg at °C)	♦6×10^{-5} (estimated) at 25 °C	[3,15]

o-Toluene sulfonamide

Density (g/cm^3 at °C)	No data found	
Vapour Density (air=1)	No data found	
Henry's Law constant (atm/m^3/mol at °C)	4.7×10^{-7}	[3,15]
Solubility (g/l water at °C)	♦Slightly soluble in water (unknown temperature) 1.62 at 25°C	[3] [15]
Partition Coefficient (log P_{ow})	♦0.84 (measured)	[3,15]
pK_a	No data found	
Flammability	No data found	
Explosivity	No data found	
Oxidising Properties	No data found	
Migration potential in polymer	Less than 0.2 mg/kg (detection limit) migrated from package material containing 0.96-3.3 mg/dm^2 to food	[20]

Emission Data

During production	No data found

Exposure Data

Aquatic environment, incl. sediment	No data found
Terrestrial environment	No data found
Sewage treatment plant	No data found
Working environment	No data found
Consumer goods	No data found
Man exposed from environment	No data found
”Secondary poisoning”	No data found
Atmosphere	No data found
Dermal	No data found

o-Toluene sulfonamide

Toxicological data

Observations in humans	♦A 2-month old infant developed no symptoms of toxicity following inadvertently uptake of a 1500 mg dose of sulfasalazine (same group as o-toluene sulphonamide)	[3]
	One patient developed seizures, coma, hypoxia, hyperglycemia, metabolic acidosis and methemoglobinemia after an oral dose of 50 mg sulfasalazine and 50 mg paracetamol. Effects (except methemoglobinemia) could be secondary to acetmenophen toxicity.	[3]
	♦Overdose of sulfasalazine result in coma in one patient and tremor in another.	[3]

Acute toxicity

Oral	No relevant data found
Dermal	No relevant data found
Inhalation	No relevant data found
Other routes	No relevant data found
Skin irritation	No relevant data found
Eye irritation	No relevant data found
Irritation of respiratory tract	No relevant data found
Skin sensitisation	No relevant data found

Subchronic and Chronic Toxicity

Oral	No relevant data found
Inhalation	No relevant data found
Dermal	No relevant data found

o-Toluene sulfonamide

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	*Salmonella typhrimurium:* ♦Negative. Histidine reverse gene mutation, Ames assay.	[7]
	Salmonella: Up to 1 mg/plate and 2.5 mg/plate. Not mutagenic. Microsome plate with and without arochlor 1254-induced rat liver 9000 XG supernatant.	[17]
	♦No test dose mentioned. Weak mutagenic effects. Modified Salmonella/microsome test.	[3]
	Saccharomyces cericisiae: Up to 1 mg/plate. No gene conversion. Test both with and without metabolic activation.	[17]
	Drosophila melanogaster: No test dose mentioned. No conclusion. Sex-linked recessive lethal gene mutation.	[7]
	0.2 µl or feeding 5 mmol. No sex-linked recessive lethal mutation.	[17]
	0.05% (3 d). Larger scale feeding study than previous study. Significant doubling of frequency of sex-linked lethal mutation.	[3]
	No test dose mentioned. Weak mutagenic effects.	[19]
Chromosome Abnormalities	*Drosophila melanogaster:* Mammalian polychromatic erythrocytes. No conclusion. Micronucleus test, chromosome aberrations.	[7]
	0.9-400 µg/ml (24 h). No increase in number of breaks, gaps, and other aberrations.	[3]
Other Genotoxic Effects	No relevant data found	
Carcinogenicity	Mouse: 2x1g/kg bw, oral and ip. No micronuclei in bone marrow cells.	[3]
	BHK 21/CL 13 cell: 0.025-2500 µg/ml. No morphological transformation in cells.	[3]

	Rat	
	♦0, 20 and 200 mg/kg bw (lifetime). No increase in incidence of malignant tumors.	[3]
	2.5, 25 and 250 mg/kg bw. Benign bladder tumor in f0 (one in control group, one in both group 2.5 and 250 mg/kg bw) and in f1 (2 in the 2.5 mg/kg bw).	[3]
	0 or 1% in drinking water or 90 mg/kg. (2 year). No difference in overall tumor incidence (2 year).	[3]
	0.15 ml NMU/N-methyl-N-nitrosourea, 2 weeks later 0, 0.08 mg o-toluenesulphonamide /kg bw in diet or 0.1% o-toluenesulphonamide in drinking water (2 years). No difference in overall tumour incidence was observed.	[3]
	♦There is limited evidence that o-toluenesulphonamide is carcinogenic when given orally to rats.	[17]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	♦In connection with assessment of saccharine and its impurities, among others o-toluenesulphonamide, it has been found that these impurities are responsible for the reproductive effects of impure saccharine.	[18]
	Rat: 250 mg/kg bw. Lower feed consumption. 2-generation study.	[3]
Teratogenicity	Rat: ♦Found to be teratogenic.	[3]
	♦0-250 mg/kg, gavage throughout gestation and lactation, also puppets. Dose-response for incidence of bladder calculi in 21-day-old pups and 105-day old rats.	[3]
	No dose mentioned, dietary treatment during mating, gestation and lactation and after weaning. Renal calculi and bladder lesions were observed in 8-day old pups.	[3]
Other Toxicity Studies	No relevant data found.	

Toxicokinetics

o-Toluene sulfonamide

Toxicokinetics	Rat: 20, 125 or 200 mg/kg bw. Single oral doses. Result: Main metabolites in the urine were 2-sulfamoylbenzyl alcohol and it sulfate or glucuronic acid conjugates (80%), n-acetyltoluene-2-sulphonamide (6%), saccharin (3%) and 2-sulfamoylbenzoic acid (2%). 79, 58 and 36% of activity recovered in urine after 24 h, 7, 14 and 33% of the dose in the urine from 24-48 h, respectively. After 7 d 4.5, 5.9 and 7% of activity was recovered from faeces.	[3]
	Human: 0.2-0.4 mg/kg bw, oral doses. Result: Excreted more slowly in humans than in rats. 50% excreted after 24 h. and 80% within 48 h. less than 1% was found in the faeces. Main urine metabolites were 2-sulfamoylbenzyl alcohol and its sulfates and glucoronic conjugates (35%), saccharin (35%), 2-sulfamoylbenzoic acid (4%) and N-acetyltouluene-2-sulphonamide (2%).	[3]

Ecotoxicity Data

Algae	No data found
Crustacean	No data found
Fish	No data found
Bacteria	No data found
Terrestrial organisms	No data found
Other toxicity information	No data found

Environmental Fate

BCF	♦0.4-2.6 2.5 (estimated)	[16] [3]
Aerobic biodegradation	Aquatic – ready: ♦0 % in 14 d, OECD 301C	 [16]
Anaerobic biodegradation	No data found	
Metabolic pathway	No data found	
Mobility	K_{oc}=68 (estimated)	[3]

o-Toluene sulfonamide

Conclusion

Physical-chemical	o-toluensulphonamide is a compound with a low water solubility, low fat solubility and a low vapour pressure.
Emission	No data found
Exposure	Not data found
Health	No data found on acute toxicity, subchronic and chronic toxicity. o-Toluensulphonamide is reported as teratogenic in rats, but no detailed descriptions of the study design is available. Only weak mutagenic activity is shown. There is limited evidence that OTSA is carcinogenic when administered orally to rats. This has been suggested as the cause of carcinogenicity of saccharin. The available data suggest that OTSA impurities at the levels normally found in commercial saccharin do not contribute to the carcinogenicity of saccharin. Based on very limited data the critical effect has been identified as possible teratogenicity. It is not possible to evaluate the data against the classification criteria for teratogenicity, as information is too sparse. Other described effects are not classifiable.
Environment	The available data on biodegradation indicate that o-toluensulphonamide do not biodegrades readily. The available BCF values indicate that o-toluensulphonamide do not bioaccumulates.

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2,2,4-trimethyl-1,3-pentandioldiisobutyrate

CAS number: 6846-50-0

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

2,2,4-trimethyl-1,3-pentandioldiisobutyrate (TXIB) is a compound with a low water solubility (1-2 mg/l). The Log P_{ow} value of 4.1 indicates lipophillic properties.

Emission

No data found.

Exposure

No data found.

Health

The available data indicate that TXIB is a substance of low toxicity. Results from animal tests do not fulfil the classification criteria with regard to acute toxicity, skin and eye irritation and skin sensitisation. Reversible liver changes were found rats in a chronic study whereas chronic toxicity testing in beagles did not reveal any significant findings.
TXIB is eliminated via urine and faeces. Half to two-thirds are excreted in urine (about two-thirds within 48 hours, about 90% by 5 days and almost complete in 10 days). Faecal elimination appeared to take 2-4 days.

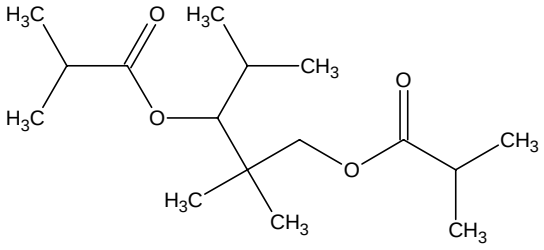
Environment

According to the available data on biodegradation there is no evidence of ready biodegradability of TXIB.

The available 50 % effect concentrations are above tested ranges, and the NOECs are assigned to the maximum tested concentration of TXIB (~1.5 mg/l).

2,2,4-trimethyl-1,3-pentandioldiisobutyrate

Identification of the substance

CAS No.	6846-50-0
EINECS No.	229-934-9
EINECS Name	1-isopropyl-2,2-dimethyltrimethylene diisobutyrate.
Synonyms	2,2,4-Trimethyl-1,3-pentanediol diisobutyrate, Kodaflex, TXIB, 2,2,4-Trimethylpentanediol diisobutyrate, (1-isopropyl-2,2-dimethyl-1,3-propandiyl) diisobutyrate.
Molecular Formula	
Structural Formula	$C_{16}H_{30}O_4$
Major Uses	No data found.
IUCLID	The substance is included in the IUCLID HPVC list.
EU classification	The compound is not included in Annex I to 67/548/EEC

Physico-chemical Characteristics

Physical Form	No data found.	
Molecular Weight (g/mole)	286.41	
Melting Point/range (°C)	-70 °C	[1a,15]
Boiling Point/range (°C)	280 °C	[1a,15]
Decomposition Temperature (°C)	No data found.	
Vapour Pressure (mm Hg at °C)	No data found (0.009 reported in [1a] but no unit given).	[1a]
Density (g/cm^3 at °C)	0.945 at 20 °C 0.94 0.944	[1a] [2] [15]

2,2,4-trimethyl-1,3-pentandioldiisobutyrate

Vapour Density (air=1)	No data found.	
Henry's Law constant (atm/m^3/mol at °C)	No data found.	
Solubility (g/l water at °C)	♦0.001-0.002 Immiscible with water	[1a] [15]
Partition Coefficient ($LogP_{ow}$)	4.1 (measured)	[1a]
pK_a	No data found.	
Flammability	No data found.	
Explosivity	No data found.	
Oxidising Properties	No data found.	
Migration potential in polymer	No data found.	

Emission Data

During production	No data found.

Exposure Data

Aquatic environment, incl. sediment	No data found.
Terrestrial environment	No data found.
Sewage treatment plant	No data found.
Working environment	No data found.
Consumer goods	No data found.
Man exposed from environment	No data found.
"Secondary poisoning"	No data found.
Atmosphere	No data found.
Dermal	No data found.

Toxicological data

2,2,4-trimethyl-1,3-pentandioldiisobutyrate

Observations in humans	No data found.	

Acute toxicity

Oral	Rat ♦ LD_{50} > 3,200 mg/kg bw.	[1a]
	Mouse LD_{50} > 6,400 mg/kg bw.	[1a]
Dermal	Guinea pig ♦ LD_{50} > 20 ml/kg.	[1a]
Inhalation	Rat ♦ 6 hour exposure to 0.12 mg/l or 5.3 mg/l. LC_{50} > 5.3 mg/l.	[1a]
Other routes	Rat ♦ LD_{50} approx. 3,200 mg/kg bw. i.p.	[1a]
Skin irritation	Guinea pig ♦ No information on test material and exposure time. Slight skin irritant when covered and more irritating when uncovered.	[1a]
Eye irritation	Rabbit ♦ 0.1 ml. Not irritating, not to be classified. (OECD 405/1990)	[1a]
Irritation of respiratory tract	No data found.	
Skin sensitisation	Guinea pig ♦ No detailed information. (Test protocol similar to OECD 406). Injection via footpad. Not sensitising.	[1a]

Subchronic and Chronic Toxicity

2,2,4-trimethyl-1,3-pentandioldiisobutyrate

Oral	Rat Albino rats. 0.1% and 1% w/w in the diet for 103 d. No significant changes. NOAEL = 0.1%, LOAEL = 1%	[1a]
	♦Sprague Dawley rats. 0.1% and 1% w/w in the diet for 52 or 99 d. Statistically significant higher liver weight in the top dose group. Liver changes appeared reversible. NOAEL = 0.1%, LOAEL = 1%.	[1a]
	Dog, beagle ♦0.1%, 0.35%, and 1% in the diet for 13 weeks. No significant findings.	[1a]
Inhalation	No data found.	
Dermal	No data found.	

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	No data found.
Chromosome Abnormalities	No data found.
Other Genotoxic Effects	No data found.
Carcinogenicity	No data found.

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	No data found.
Teratogenicity	No data found.
Other Toxicity Studies	No data found.

Toxicokinetics

Toxicokinetics	Metabolic studies in rats indicated that hydrolysis to the parent glycol (TMPD) is a major pathway in the disposal of the diisobutyrate. The substance is rapidly absorbed from the gut. No elimination via lungs. From half to two-thirds excreted in urine (about two-thirds within 48 hours, about 90% by 5 d and almost complete in 10 d). Faecal elimination appeared to take 2-4 d.	[1a]

2,2,4-trimethyl-1,3-pentandioldiisobutyrate

Ecotoxicity Data

Algae	No data found.	
Crustacean	*Asellus intermedius*:	
	LC_{50}(96h)>1.55 mg/l	[1a]
	NOEC(96h)=1.55 mg/l	[1a]
	Daphnia magna (fw):	
	LC_{50}(96h)>1.46 mg/l	[1a]
	NOEC(96h)=1.46 mg/l	[1a]
	Gammarus fasciatus:	
	LC_{50}(96h)>1.55 mg/l	[1a]
	NOEC(96h)=1.55 mg/l	[1a]
Fish	*Pimephales promelas* (fw):	
	LC_{50}(96h)>1.55 mg/l	[1a]
	NOEC(96h)=1.55 mg/l	[1a]
Bacteria	No data found.	
Terrestrial organisms	No data found.	
Other toxicity information	*Dugesia tigrina*:	
	LC_{50}(96h)>1.55 mg/l	[1a]
	NOEC(96h)=1.55 mg/l	[1a]
	Lumbriculus variegatus:	
	LC_{50}(96h)>1.55 mg/l	[1a]
	NOEC(96h)=1.55 mg/l	[1a]
	Helisoma trivolvis:	
	LC_{50}(96h)>1.55 mg/l	[1a]
	NOEC(96h)=1.55 mg/l	[1a]

Environmental Fate

BCF	No data found.	
Aerobic biodegradation	Aquatic – other tests:	
	99.9 % at 650 mg/l (incomplete information)	[1a]
Anaerobic biodegradation	No data found.	
Metabolic pathway	No data found.	
Mobility	No data found.	

2,2,4-trimethyl-1,3-pentandioldiisobutyrate

Conclusion

Physical-chemical	2,2,4-trimethyl-1,3-pentandioldiisobutyrate (TXIB) is a compound with a low water solubility (1-2 mg/l). The Log P_{ow} value of 4.1 indicates lipophillic properties.
Emission	No data found.
Exposure	No data found.
Health	The available data indicate that TXIB is a substance of low toxicity. Results from animal tests do not fulfil the classification criteria with regard to acute toxicity, skin and eye irritation and skin sensitisation. Reversible liver changes were found rats in a chronic study whereas chronic toxicity testing in beagles did not reveal any significant findings. TXIB is eliminated via urine and faeces. Half to two-thirds are excreted in urine (about two-thirds within 48 hours, about 90% by 5 days and almost complete in 10 days). Faecal elimination appeared to take 2-4 days.
Environment	According to the available data on biodegradation there is no evidence of ready biodegradability of TXIB. The available 50 % effect concentrations are above tested ranges, and the NOECs are assigned to the maximum tested concentration of TXIB (~1.5 mg/l).

References

1 European Commission Joint Research Centre (1996): International Uniform Chemical Information Database. IUCLID CD-ROM – Existing Chemicals – 1996.

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http://toxnet.nlm.nih.gov

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http://toxnet.nlm.nih.gov

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Epoxidized soybean oil

CAS number: 8013-07-8

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

Sufficient data not available.

Emission

No data found

Exposure

No data found

Health

ESBO is only slightly acute toxic. In the acute oral tests LD_{50} to rat ranged between 21,000-40,000 mg/kg bw and were not irritating to skin.
ESBO was not mutagenic in Ames test. Based on the limited data available ESBO was not found to be a potential carcinogen or to exhibit reproductive toxicity or teratogenitity. In reproductive toxicity tests in mouse and rat the NOAEL for the parental group was 1,000 mg/kg bw and the NOAEL for the F1 offspring were 1,000 mg/kg bw.

Environment

According to the available biodegradation data there is good evidence of ready biodegradability of epoxidized soybean oil.
The available ecotoxicological data indicates that epoxidized soybean oil is toxic to crustaceans.

Epoxidized soybean oil

Identification of the substance

CAS No.	8013-07-8	
EINECS No.	232-391-0	
EINECS Name	Soybean oil, epoxidized	
Synonyms	Soybean oil epoxidized, Epoxidised soyabean oil, ESBO, Epoxidised soy bean oil.	
Molecular Formula	No data found	
Structural Formula	No data found	
Major Uses	Softener. Solvent. Construction material additive. Viscosity adjusters. Stabiliser. Plasticiser processing aid.	[1] [1] [1] [1] [1] [3]
IUCLID	The substance is included in the IUCLID HPVC list.	
EU classification	The compound is not included in Annex I to 67/548/EEC	

Physico-chemical Characteristics

Physical Form	No data found	
Molecular Weight (g/mole)	No data found	
Melting Point/range (°C)	No data found	
Boiling Point/range (°C)	No data found	
Decomposition Temperature (°C)	No data found	
Vapour Pressure (mm Hg at °C)	No data found	
Density (g/cm^3 at °C)	0.994-0.998	[1]
Vapour Density (air=1)	No data found	
Henry's Law constant ($atm/m^3/mol$ at °C)	No data found	

Epoxidized soybean oil

Solubility (g/l water at °C)	Low (unknown temperature)	[1]
Partition Coefficient (log P_{ow})	> 6 (estimated)	[1]
pK_a	No data found	
Flammability	No data found	
Explosivity	No data found	
Oxidising Properties	No data found	
Migration potential in polymer	No data found	

Emission Data

During production	No data found

Exposure Data

Aquatic environment, incl. sediment	No data found
Terrestrial environment	No data found
Sewage treatment plant	No data found
Working environment	No data found
Consumer goods	No data found
Man exposed from environment	No data found
”Secondary poisoning”	No data found
Atmosphere	No data found
Dermal	No data found

Toxicological data

Observations in humans	♦Asthma developed in a worker exposed to vapour from heated polyvinyl chloride film containing ESBO. Challenge with ESBO vapour of unspecified concentration produced asthmatic symptoms within 5 min.	[1]

Epoxidized soybean oil

Acute toxicity

Oral	Rat: ♦21,000-40,000 mg/kg bw. Single dose of 5.000 mg/kg caused dispnoea and diarrhoea. (must be 5,000). ♦ LD_{50}>5,000 mg/kg bw.	[1] [1]
Dermal	Rabbit: ♦No dose mentioned (24 h) occlusion. LD_{50}>20,000 mg/kg bw.	[1]
Inhalation	No data found	
Other routes	No data found	
Skin irritation	Rabbit: ♦Moderately irritating (24 h) occlusion. Slightly irritating. EPA, Federal reg., Vol 43, No. 163	 [1] [1]
Eye irritation	Rabbit: 0.5 ml. Not irritating. Instillation of 0.5 ml of undiluted substance. ♦Not irritating. EPA, Federal Register, Vol. 43, No. 163.	 [1] [1]
Irritation of respiratory tract	No data found	
Skin sensitisation	Guinea pig: ♦Induction phase of 8 intracutaneous injection of diluted product (no further information). 3 weeks later challenge with 0,1 ml of 0.1% Reoplast 39%. Rechallange after 2 weeks with patch test 30% Reoplast 39 in 1:1 propylene glycol:saline cover for 24 h, 20 animals/group. No sensitisation was observed. Optimisation test.	 [1]

Epoxidized soybean oil

Subchronic and Chronic Toxicity

Oral	Rat	
	♦0.25% and 2.5% Reoplast 39 (2 years) oral feed, 48 animals/dose group. NOAEL: Approx. 1.3 mg/kg bw. Slight injury in uterus at 2.5% (ca. 1.4 g/kg bw/d).	[1]
	♦Approx. 10 g/kg bw/d, epoxide numbers 14.6-111.5 (10 w). Slow growth, death in groups receiving compound with epoxide number 49.7 or more. Water intake increased with epoxide number while food intake and protein utilisation decreased. Feeding with epoxy number 105 and 111.5 - severe degeneration of testes. Fatty degeneration in the controls and in the group fed ESBO with epoxide numbers 14.6-49.7.	[1]
	♦1.4 g/kg/application, 2 applications/w (16 months). NOAEL= 1,400 mg/kg bw.	[1]
	Dog	[1]
	Up to 5% paraplex G-60 and paraplex G-62 (ca. 1.25 g/kg/d)(one year) oral feed. Food intake and bw decrease (5%) in all dose groups. Slight liver change in 5% paraplex G-62.	[1]
	1.4 g/kg (12 months) 2 applications/w. NOAEL= 1,400 mg/kg.	
Inhalation	No data found	
Dermal	No data found	

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	♦*Salmonella typhimurium:*	
	Up to 2,025 µg/plate. Test strain: TA98, TA100, TA1535, TA1537. No mutagenicity was observed. Ames test, Ciba methode nach B. N. Ames 1973 u. 1975 with and without metabolic activation.	[1]
	4, 20, 100 ,500, 2,500, 12,500 µg/plate. Test strain: TA98, TA100, TA1535, TA1537 and TA 1538. No mutagenicity was observed. Ames test, Henkel-method "*Salmonella typhimurium* reverse mutation assay" with and without metabolic activation, GLP.	[1]
	Up to 5,000 µg/plate. Test strain: TA98, TA100, TA1535, TA1537 and TA102. No mutagenicity was observed. Ames test, Siehe RE with and without metabolic activation. GLP.	[1]

	Mouse: ♦Up to 5,000 µg/l. No mutagenicity was observed. Mouse lymphona assay , Siehe RE, with and without metabolic activation., GLP	[1]
Chromosome Abnormalities	No data found	
Other Genotoxic Effects	Humane lymphocytes: No doses specified (20 to 44 h without, 3 h with metabolic activation). No evidence of clastogenic effect or induced aneuploidy. Cytogenetic assay Siehe Re.	[1]
Carcinogenicity	Mouse: No dose specified undiluted ESBO (whole life) 3timesw, 40 animals. No skin tumors.	[1]
	Total dose 2.15 g/kg bw (3 w), i.p. once/w. No incidence of lung tumors after 16 weeks.	[1]
	Rat: ♦Up to 2.5% (1.4 g/kg bw/d) Paraplex G-60 and Paraplex G-62 (2 years) oral feed. No evidence of carcinogenicity.	[1]
	Up to 5% paraplex G-60 and Paraplex G-62 (1 or 2 years) oral feed. No evidence of carcinogenicity.	[1]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat: ♦100, 300, 1,000 mg/kg bw/d (21 d post-partum) gavage. NOAEL, parental = 1,000 mg/kg bw, NOAEL, F1 offspring = 1,000 mg/kg bw. OECD 415.	[1]
	20% (ca. 10 g/kg bw/d; 7 w), epoxide number 15 and 50. No histological changes of the testes in animals treated with epoxide number 15 to 50. Severe degeneration in testes of animals tested with ESBO with epoxide number between 105 or 111.5.	[1]
Teratogenicity	Rat: ♦100, 300, 1,000 mg/kg bw/d (6. to 15. day of the pregnancy) gavage, 25 females/dose group. NOAEL, parental = 1,000 mg/kg bw, NOAEL, F1 offspring = 1,000 mg/kg bw. OECD 414.	[1]
Other Toxicity Studies	No data found	

Toxicokinetics

Toxicokinetics	No data found

Epoxidized soybean oil

Ecotoxicity Data

Algae	No data found	
Crustacean	*Artemia salina*: EC_{50}(24h) = 240 mg/l, unspecified static test	[1,11]
	Daphnia magna: ♦ EC_{50}(24h) = 8 mg/l, Dir. 87/302/EEC, part C NOEC(24h) = 0.7 mg/l, Dir. 87/302/EEC, part C	[1] [1]
Fish	*Leuciscus idus* (fw): ♦ LC_{50}(48h) = 900 mg/l, DIN 38412-L15 LC_{50}(48h) = >10,000 mg/l, DIN 38412-L15	[1] [1]
Bacteria	*Activated sludge*: EC_{50}(3h)>100 mg/l, OECD 209	[1]
	Pseudomonas putida: EC_0(0.5h)>10,000 mg/l, DIN 38412-L27	[1]
Terrestrial organisms	No data found	
Other toxicity information	Water transpiration of *Vicia faba* (pea) sprayed with a 10 % suspension of epoxidized soybean oil was reduced by 30 %. A slight increase in grain yield (g dry weight/plant) of maize or no effect (dependent on water supply of plants) when sprayed onto soil or plant was observed itself as a 0,05 - 0,1 % suspension was further observed.	[1]

Environmental Fate

BCF	No data found	
Aerobic biodegradation	Aquatic – ready biodegradability tests: ♦ 79 % at 10 mg/l in 28 d, OECD 301 B ♦ 78 % at 2 mg/l in 28 d, OECD 301 D	 [16] [17]
	Aquatic – other tests: 20 % at 10 mg/l in 20 d, unspecified BOD test	 [1]
Anaerobic biodegradation	No data found	
Metabolic pathway	No data found	
Mobility	No data found	

Epoxidized soybean oil

Conclusion

Physical-chemical	No data found
Emission	No data found
Exposure	No data found
Health	ESBO is only slightly acute toxic. In the acute oral tests LD_{50} in rats ranged between 21,000-40,000 mg/kg bw. ESBO was only slightly irritating to skin. ESBO was not mutagenic in Ames test. Based on the limited data available ESBO was not found to be carcinogen or to exhibits reproductive toxicity or teratogenitity. In reproductive toxicity tests in mouse and rat the NOAEL for the parental group were 1,000 mg/kg bw and the NOAEL for the F1 offspring were 1,000 mg/kg bw.
Environment	According to the available biodegradation data there is good evidence of ready biodegradability of epoxidized soybean oil. The available ecotoxicological data indicates that epoxidized soybean oil is toxic to crustaceans.

References

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13 Lide, D.R. (ed). CRC Handbook of Chemistry and Physics. 72nd ed. Boca Raton, FL: CRC Press 1991-1992.

14 Petersen, J., H. (1999): Forurening af fødevarer med blødgører – Migration fra plast og generel baggrundsforurening. Ph.D Thesis. The Danish Veterinary and Food Administration.

15 Ciba Additive GmbH Lambertheim (1988) not published. Quoted in ref 1.

16 Henkel KGaA (Pruefnr. 7014), not published. Quoted in ref. 1.

Dipropyleneglycol dibenzoate

CAS number: 27138-31-4

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

Dipropyleneglycol dibenzoate is a compound with low water solubility (15 mg/l) and a low vapour pressure. The estimated Log P_{ow} value of 3.88 indicates lipophillic properties.

Emission

No data found.

Exposure

No data found.

Health

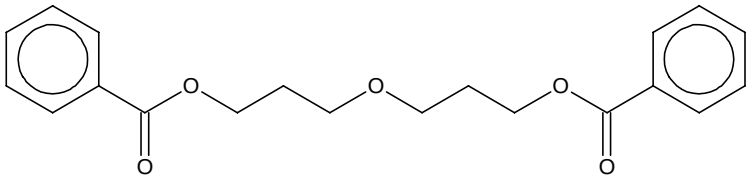
No data found.

Environment

No data found.

Dipropyleneglycol dibenzoate

Identification of the substance

CAS No.	27138-31-4
EINECS No.	248-258-5
EINECS Name	Oxydipropyl dibenzoate
Synonyms	Propanol, oxybis-, dibenzoate
Molecular Formula	$C_{20}H_{22}O_5$
Structural Formula	
Major Uses	No data found
IUCLID	The substance is not included in the IUCLID HPVC list.
EU classification	The compound is not included in Annex I to 67/548/EEC

Physico-chemical Characteristics

Physical Form	No data found	
Molecular Weight (g/mole)	342.4	
Melting Point/range (°C)	No data found	
Boiling Point/range (°C)	No data found	
Decomposition Temperature (°C)	No data found	
Vapour Pressure (mm Hg at °C)	♦4.6×10^{-7} at 25 °C	[15]
Density (g/cm^3 at °C)	No data found	
Vapour Density (air=1)	No data found	
Henry's Law constant (atm/m^3/mol at °C)	1.38×10^{-8} at 25 °C	[15]

Dipropyleneglycol dibenzoate

Solubility (g/l water at °C)	♦0.015 (at 25 °C)	[15]
Partition Coefficient (log P_{ow})	♦3.88 (estimated)	[15]
pK_a	No data found	
Flammability	No data found	
Explosivity	No data found	
Oxidising Properties	No data found	
Migration potential in polymer	No data found	

Emission Data

During production	No data found

Exposure Data

Aquatic environment, incl. sediment	No data found
Terrestrial environment	No data found
Sewage treatment plant	No data found
Working environment	No data found
Consumer goods	No data found
Man exposed from environment	No data found
”Secondary poisoning”	No data found
Atmosphere	No data found
Dermal	No data found

Toxicological data

Observations in humans	No data found.

Dipropyleneglycol dibenzoate

Acute toxicity

Oral	No data found.
Dermal	No data found.
Inhalation	No data found.
Other routes	No data found.
Skin irritation	No data found.
Eye irritation	No data found.
Irritation of respiratory tract	No data found.
Skin sensitisation	No data found.

Subchronic and Chronic Toxicity

Oral	No data found.
Inhalation	No data found.
Dermal	No data found.

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	No data found.
Chromosome Abnormalities	No data found.
Other Genotoxic Effects	No data found.
Carcinogenicity	No data found.

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	No data found.
Teratogenicity	No data found.
Other Toxicity Studies	No data found.

Dipropyleneglycol dibenzoate

Toxicokinetics

Toxicokinetics	No data found.

Ecotoxicity Data

Algae	No data found.
Crustacean	No data found
Fish	No data found
Bacteria	No data found
Terrestrial organisms	No data found
Other toxicity information	No data found

Environmental Fate

BCF	No data found
Aerobic biodegradation	No data found
Anaerobic biodegradation	No data found
Metabolic pathway	No data found
Mobility	No data found

Conclusion

Physical-chemical	Dipropyleneglycol dibenzoate is a compound with low water solubility (15 mg/l) and a low vapour pressure. The estimated Log P_{ow} value of 3.88 indicates lipophillic properties.
Emission	No data found
Exposure	No data found
Health	No data found
Environment	No data found

Dipropyleneglycol dibenzoate

References

1 European Commission Joint Research Centre (1996): International Uniform Chemical Information Database. IUCLID CD-ROM – Existing Chemicals – 1996.

1a European Commission Joint Research Centre (2000): International Uniform Chemical Information Database. IUCLID CD-ROM. Year 2000 Edition. ISBN 92-828-8641-7.

2 Chemfinder – Cambridge Soft.
http://www.chemfinder.com

3 HSDB - Hazardous Substances Data Bank
http://toxnet.nlm.nih.gov

4 IRIS - Integrated Risk Information System
http://toxnet.nlm.nih.gov

5 CCRIS - Chemical Carcinogenesis Research Information System
http://toxnet.nlm.nih.gov

6 NTP – National Toxicology Program, Chemical Health & Safety Data
http://ntp-server.niehs.nih.gov

7 Genetox - Genetic Toxicology
http://toxnet.nlm.nih.gov

8 Chemfate - Syracuse Research Corporation. Environmental Fate Database
http://esc.syrres.com

9 Biodeg - Syracuse Research Corporation. Environmental Fate Database
http://esc.syrres.com

10 Betratergremium für umweltrelevante Altstoffe (1996): *Di-(2-ethylhexyl)adipat, BUA-Stoffbericht 196.* S. Hirzel, Frankfurt am Main.

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12 Verschueren, K. (1996) Handbook of Environmental Data on Organic Chemicals. 3rd Ed. Van Nostrand Reinhold. New York.

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14 Petersen, J., H. (1999): Forurening af fødevarer med blødgører – Migration fra plast og generel bag-grundsforurening. Ph.D Thesis. The Danish Veterinary and Food Administration.

15 PhysProp - Syracuse Research Corporation. Interactive PhysProp Database
http://esc.syrres.com/interkow/physdemo.htm

Dioctyl sebacate

CAS number: 122-62-3

Physical-chemical, emission, exposure, health and environment data

Summary

Physical-chemical

Dioctyl sebacate is a compound with a low estimated vapour pressure and water solubility.
The estimated Log P_{ow} value indicates that dioctyl sebacate may bioaccumulate.

Emission

No data found

Exposure

No data found

Health

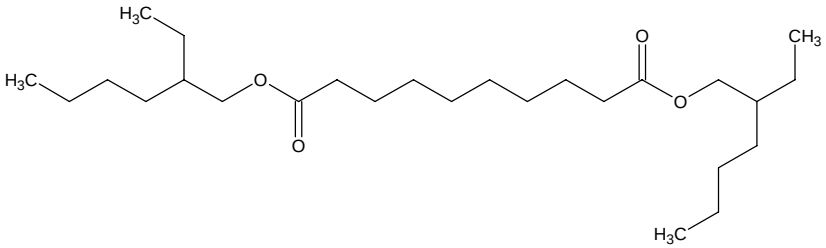
Only a limited data set were found.
The acute toxicity for rats was as LD_{50} 1,280 mg/kg bw and for rabbit 540 mg/kg bw.
Based on the available data dioctyl sebacate is not considered a potential carcinogen, and has not been shown to produce any reproductive toxicity.

Environment

No data found

Dioctyl sebacate

Identification of the substance

CAS No.	122-62-3	
EINECS No.	204-558-8	
EINECS Name	Bis(2-ethylhexyl) sebacate	
Synonyms	Decanedionic acid bis(2-Ethylhexyl) ester, octyl Sebacate, sebacic acid bis(2-ethylhexyl) ester, bis(2-ethylhexyl) sebacate, bisoflex dos, DOS, 2-ethylhexyl sebacate, 1-hexanol 2-ethyl-sebacate, monoplex dos, octoil s, PX 438, Staflex dos, Plexol 201, bis(2-ethylhexyl) de-canedioate, Edenol 888, Ergoplast sno, Reolube dos, DEHS.	
Molecular Formula	$C_{26}H_{50}O_4$	
Structural Formula		
Major Uses	Synthetic lubricant for reaction motor Plasticiser for poly(methyl methylacrylate) and cyclo-nite.	[3] [3]
IUCLID	The substance is not included in the IUCLID HPVC list.	
EU classification	The compound is not included in Annex I to 67/548/EEC	

Physico-chemical Characteristics

Physical Form	Pale straw coloured liquid. Oily colourless liquid. Pale yellow liquid. Clear light coloured liquid.	[3] [3] [6] [6]
Molecular Weight (g/mole)	426.68	
Melting Point/range (°C)	-67 °C ♦–48 °C	[2] [3,6]
Boiling Point/range (°C)	248 at 4 mm Hg	[2,6] [3]

Dioctyl sebacate

	256 °C at 5 mm Hg	
Decomposition Temperature (°C)	No data found	
Vapour Pressure (mm Hg at °C)	♦ 1.0×10^{-7} (estimated, 25 °C)	[15]
Density (g/cm^3 at °C)	0.914 0.912 at 25 °C 0.91 at 25 °C	[2] [3] [6]
Vapour Density (air=1)	14.7	[3]
Henry's Law constant ($atm/m^3/mol$ at °C)	No data found	
Solubility (g/l water at °C)	Insoluble (temperature unknown) ♦ 3.5×10^{-7} (estimated, 25 °C)	[6] [15]
Partition Coefficient (log P_{ow})	♦ 10.08 (estimated)	[15]
pK_a	No data found	
Flammability	Slightly flammable when exposed to heat.	[3]
Explosivity	No data found	
Oxidising Properties	No data found	
Migration potential in polymer	76-137 mg/kg Dioctyl sebacate	[17]

Emission Data

During production	No data found

Exposure Data

Aquatic environment, incl. sediment	No data found
Terrestrial environment	No data found
Sewage treatment plant	No data found
Working environment	No data found
Consumer goods	No data found
Man exposed from environment	No data found

”Secondary poisoning”	No data found	
Atmosphere	No data found	
Dermal	No data found	

Toxicological data

Observations in humans	Volunteers did not generate sensitisation during 48 hour covering and patch tests.	[16]
	DOS aerosols have been used to demonstrate particle deposition in lung and respiratory tract without apparently producing overt toxic effects.	

Acute toxicity

Oral	Rat ♦ LD_{50}=1,280 mg/kg	[6]
	LD_{50}(rat)=1,700 mg/kg bw	[16]
	LD_{50}(mouse)=9,500 mg/kg bw	[16]
	Exposure to DOS may produce reduced coordination, laboured breathing and diarrhoea, with tissue damage in the liver, spleen, brain and heart.	[16]
Dermal	LD_{50}(guinea-pig) > 10 g/kg bw	[16]
Inhalation	♦ No adverse effects were seen in a 13-week study where 12 rats exposed to 250 mg/m^3.	[16]
	No seen effects on lung or liver below saturating concentrations but saturated mist may cause lung toxicity. When DOS is heated to 371 °C decomposition products can lead to death of rabbits and rats.	
Other routes	Rat ♦ LD_{50}= 900 mg/kg , i.v.	[16]
	Rabbit ♦ LD_{50}= 540 mg/kg, i.v.	[16]
Skin irritation	♦ Not a skin irritant or absorbed through skin.	[3]
	Not a skin irritant during 48 hour tests	[16]

Eye irritation	Above 60 mg/m^3 for 1 minute it is irritating	[16]
Irritation of respiratory tract	Above 60 mg/m^3 for 1 minute it is irritating	[16]
Skin sensitisation	Not sensitising in rabbits	[16]

Subchronic and Chronic Toxicity

Oral	Rat 1 g/kg bw/day for 3 weeks, increased liver weight, peroxisome proliferation, increased levels of peroxisome enzymes.	[16]
Inhalation	Rat ♦Exposed to air bubbled through a column of liquid at 100 °C (6 h). No toxic effects and no mortality were observed.	[3]
Dermal	No data found	

Mutagenicity, Genotoxicity and Carcinogenicity

Mutagenicity	♦*Salmonella typhimurium* No dose specified. Test strains: TA100, TA 1535, TA1537, TA98. No mutagenicity were observed. Preincubation with and without metabolic activation system.	[5]
Chromosome Abnormalities	No data found	
Other Genotoxic Effects	No data found	
Carcinogenicity	Rat 200 mg/kg bw (19 months). Result: No effects observed. No carcinogenic potential.	[3]
	♦Rats fed with a diet containing 10 mg/kg bw for up to 19 month showed no carcinogen effects and the reproduction were normal in a 4 generation study of rats fed with about 10 mg/kg bw.	[16]

Reproductive Toxicity, Embryotoxicity and Teratogenicity

Reproductive Toxicity	Rat 200 mg/kg bw (19 months). No effects observed in growth, pathology, reproduction, or during parturition or nursing in several generations.	[16]

	♦Rats fed with a diet containing 10 mg/kg bw for up to 19 month showed that the reproduction were normal in a 4 generation study of rats fed with about 10 mg/kg bw.	[16]
Teratogenicity	No data found	
Other Toxicity Studies	No data found	

Toxicokinetics

Toxicokinetics	Not absorbed through skin.	[3]

Ecotoxicity Data

Algae	No data found
Crustacean	No data found
Fish	No data found
Bacteria	No data found
Terrestrial organisms	No data found
Other toxicity information	No data found

Environmental Fate

BCF	No data found
Aerobic biodegradation	No data found
Anaerobic biodegradation	No data found
Metabolic pathway	No data found
Mobility	No data found

Conclusion

Dioctyl sebacate

Physical-chemical	Dioctyl sebacate is a compound with a low estimated vapour pressure and water solubility. The estimated Log P_{ow} value indicates that dioctyl sebacate may bioaccumulate.
Emission	No data found
Exposure	No data found
Health	Only a limited data set were found. The acute toxicity for rats was as LD_{50} 1,280 mg/kg bw and for rabbit 540 mg/kg bw. Based on the available data dioctyl sebacate is not considered a potential carcinogen, and has not been shown to produce any reproductive toxicity.
Environment	No data found

References

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