EUROPEAN COMMISSION

JOINT RESEARCH CENTRE

Institute for Health and Consumer Protection
European Chemicals Bureau
I-21020 Ispra (VA) Italy

1,2-BENZENEDICARBOXYLIC ACID, DI-C9-11-BRANCHED ALKYL ESTERS, C10-RICH

and

DI-"ISODECYL" PHTHALATE

(DIDP)

CAS Nos: 68515-49-1 and 26761-40-0

EINECS Nos: 271-091-4 and 247-977-1

Summary Risk Assessment Report

2003 **Special Publication I.03.103**

1,2-BENZENEDICARBOXYLIC ACID, DI-C9-11-BRANCHED ALKYL ESTERS, C10-RICH

and

DI-"ISODECYL" PHTHALATE

(DIDP)

CAS Nos: 68515-49-1 and 26761-40-0

EINECS Nos: 271-091-4 and 247-977-1

SUMMARY RISK ASSESSMENT REPORT

Final report, 2003

France

The French rapporteur for the risk evaluation of 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich and di-"isodecyl" phthalate is the Ministry of the Environment with the Ministry of Health and the Ministry of Work.

The scientific work on this report has been prepared by:

INERIS
DRC
Parc Technologique ALATA
BP N° 2
60550 Verneuil en Halatte
FRANCE

Institut national de recherche et de sécurité (INRS)
Service du Contrôle des Produits
30, rue Olivier Noyer
75680 PARIS CEDEX 14
FRANCE

Centre Anti-poison de Lille
5, avenue Oscart Lambret
59037 Lille Cedex
FRANCE

Date of Last Literature Search:	**2001**
Review of report by MS Technical Experts finalised:	**2001**
Final report:	**2003**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substances 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich and di-"isodecyl" phthalate that has been prepared by France in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

CONTENTS

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

In this risk assessment report two di "isodecyl" phthalate products (hereafter referred to as DIDP) are evaluated. There are two different CAS numbers. Following specific information from the European Council for Plasticisers & Intermediates, these two products are prepared essentially from the same feed, through an identical olefin oligomerisation process and through similar alcohol manufacturing and phthalate esterification processes. The two phthalates are therefore considered fully interchangeable within their whole range of the market end-uses. Only one risk assessment is performed for the two compounds.

CAS Number:	68515-49-1 and 26761-40-0
EINECS Number:	271-091-4 and 247-977-1
IUPAC Name:	1,2-Benzenedicarboxylic acid, di-C9-11 branched alkyl esters, C_9 rich and di-"isodecyl" phthalate
Molecular weight:	Average 446.68
Molecular formula:	$C_{28}H_{46}O_4$ (average)

1.2 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value
Melting point	-53 to -39°C (av. -45°C)
Boiling point	> 400°C
Density	0.966 at 20°C
Vapour pressure	$5.1 \cdot 10^{-5}$ Pa at 25°C
Water solubility	0.2 µg/l at 20°C
Henry's law constant	114 Pa · m^3/mol
Log Kow	8.8
Flash point	> 200°C
Autoflammability	ca. 380°C
Viscosity	ca. 130 mPa · s

1.3 CLASSIFICATION

No classification.

2 GENERAL INFORMATION ON EXPOSURE

There are currently four producers of DIDP in the EU. The estimated consumption volume in 1994 is ca. 200,000 t/a. An increase of the consumption of DIDP is to be expected over the following years. Approximately 95% of DIDP are used in PVC as a plasticiser. The remaining 5% are used in non-PVC applications. More than half of the DIDP used in non-PVC applications involves polymer-related uses (e.g. rubbers). The remaining DIDP is used in non-polymer applications including anti-corrosion paints, anti-fouling paints, sealing compounds and textile inks.

For the estimation of the releases to the environment through articles containing DIDP, the amount of substance included in articles being used outdoors or indoors, as well as the service life of the respective articles was estimated, as shown in **Table 2.1**.

Table 2.1 Volumes of DIDP in different articles and their respective lifetimes

Application	DIDP [t/a]	Technical lifetime
In-door application		
Wires & cables	27,400	30
Floor	20,055	20
Out-door application		
Roofing material	430	20
Roofing (coil coating)	2,150	10
Wires & cables	27,400	30
Coated fabric	9,060	10
Hoses & Profiles	2,590	10
Car under-coating	14,516	14
Shoe soles	15,843	5
Sealings	520	20
Paints & lacquers	1,040	7

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

As DIDP is an isomeric mixture, the fate and behaviour of the substance cannot be determined with accuracy. Each component of the mixture would tend to have different characteristics concerning its fate and behaviour in the environment. Nevertheless, an overall picture can be drawn, as presented below.

The major characteristics of DIDP relevant for the exposure assessment are:

- no hydrolysis in water,
- readily degradable but failing the 10-day window criterion; (based on results from simulation tests performed with diethylhexyl phthalate (DEHP), representative half-lives in surface water, soil and sediment of respectively 50, 300 and 3,000 days could be estimated for DIDP),
- an estimated atmospheric half-life of 0.6 day.

The high log Kow values imply a high potential for bioaccumulation, strong sorption to sewage sludge, soils and sediments and very low mobility in soil (Koc values of 111,000-611,000 l/kg). Bioconcentration factors (whole body values ranging from <14.4 to 4,000) have been reported with certain freshwater organisms.

Based on the model SIMPLETREAT, it is estimated that in sewage treatment plants, 84.8% of any discharged DIDP will be adsorbed on to sludge, 3.9% will be degraded and 3.2% will be stripped to air, with the remaining 8.1% being released with the aqueous effluent.

Environmental releases

Releases from production have been estimated from site-specific information. Industry information has also been used to estimate emissions from the manufacture of polymeric material. No specific information was found for the use of DIDP paints, sealing compounds and textile inks, and so default release factors from the EU Technical Guidance Document (TGD) were used.

Furthermore, the releases from polymeric articles during their use as well as during their disposal were estimated in a very preliminary manner. The overall releases are shown in **Table 3.1**.

Table 3.1 Total releases to wastewater, surface water and air

Life-cycle step	Waste water (t/a)		Surface water (t/a)		Air (t/a)	
	continental	regional	continental	regional	continental	regional
Production	63	150	-	-	-	0.25
Distribution	15.7	1.8	-	-	-	-
Processing in PVC	66.1	7.3			66.1	7.3
Processing in non-PVC polymers	10.6	1.18			10.6	1.18

Table 3.1 continued overleaf

Table 3.1 continued Total releases to wastewater, surface water and air

Life-cycle step	Waste water (t/a)		Surface water (t/a)		Air (t/a)	
	continental	regional	continental	regional	continental	regional
Use in anti-corrosion paints Formulation Application	 4.7 0.47	 0.52 0.05	 - -	 - -	 - -	 - -
Use in anti-fouling paints Formulation Application	 - -	 - -	 - -	 - -	 - -	 - -
Use in inks for textiles Formulation Application	 4.68 0.47	 0.52 0.05	 - -	 - -	 1.17 -	 0.13 -
Exterior and interior use of DIDP-containing PVC-products	400	44	251.7	28	70.6	7.84
Use of DIDP-containing non-PVC products	13.4	1.5	8.43	0.94	2.36	0.26
Applied anti-corrosion paints containing DIDP	-	-	9.2	1.0	0.17	0.018
Applied anti-fouling paints containing DIDP	-	-	-	-	-	-
Applied sealings containing DINP	-	-	2.6	0.29	0.047	0.005
Use of DIDP-treated textiles	90	9.9	-	-	0.047	0.005
Disposal of end-products	-	-	1,314	146	48.8	5.45
Total	**674**	**217.3**	**1,585**	**176.2**	**200**	**22.4**

Environmental concentrations

The methods in the TGD were used to estimate predicted environmental concentrations (PECs) for water, sediment, sewage treatment plants, air, soil and biota. **Table 3.2** shows the PECs calculated for the various stages of the life cycle of DIDP, including regional concentrations in the different environmental compartments. The calculated levels in air are very low for all life-cycle stages and so are not represented here. The majority of the PECs are consistent with measured data.

Table 3.2 PECs calculated for the various stages of the life cycle of DIDP

Life cycle step		PEClocal$_{water}$ [µg/l]	PEClocal$_{sed}$ [µg/kg dw]	PEClocal$_{soil}$ [µg/kg dw]	PECbiota$_{aquatic}$ [mg/kg ww]	PECbiota$_{soil}$ [mg/kg ww]
Production *(highest release)*		45	718,000	-	15.4	0.11
Processing in PVC		16.4	247,000	16,400	31.4	6.1
Processing in non-PVC		9.15	128,000	8,500	19.3	3.1
Use in anti-corrosion paints	I * II **	6 1.25	79,000 1,000	5,300 negligible	6.34 negligible	0.02 negligible
Use in anti-fouling paints		5	60,000	4,000	12.4	1.5
Use in sealing compounds		6	79,000	5,300	14.5	2.0
Use in inks for textiles	I II	6 1.3	79,000 2,200	5,300 150	14.5 6.46	2.0 0.05

* formulation
** processing

3.2 EFFECTS ASSESSMENT

Aquatic compartment (including microorganisms and benthic organisms)

Acute toxicity tests have been performed with several fish and invertebrate species. No effects were seen at the concentrations up to and above the solubility limit of the substance. No long-term test results with fish exposed via the water phase are available, but a two-generation feeding study has been carried out with *Oryzias latipes,* in which no impact on any populational parameter was observed. Apart from physical effects (e.g. entrapment), no effects were seen in reproduction studies with *Daphnia magna*. Furthermore, no impact on the growth of algae was observed in several species up to and beyond the solubility limit of DIDP.

Similarly, no inhibition of the respiration of activated sludge was observed.

Several laboratory assays were performed on sediment dwellers, showing no effects up to the highest tested concentrations (3,000 – 10,000 mg/kg dw). Furthermore, the hatching and development of frog eggs in contact with sediment containing DIDP up to concentrations of 600 mg/kg dw was not affected. As it could be concluded that DIDP does not have adverse effects towards aquatic or benthic organisms at the limit of water solubility in laboratory tests, no PNECs could be derived.

Potential for endocrine disruption

The most relevant test result is from the multigeneration study with *Oryzias latipes.* There were no statistically significant changes in mortality or fecundity between the treatment groups. There was no reduced egg production. Evaluation of F1 and F2 embryos showed normal development. The male to female ratios (3:1) in all groups were similar. Phenotypic gender classification of male and female fish was histopathologically confirmed to be 100% correct. Ale somatic gonadal index and liver somatic index were not significantly different in any group. Based on these data there does not appear to be an impact on any populational parameter from chronic exposure to DIDP on fish.

Atmosphere

Some phthalates, especially dibutylphthalate (DBP) have shown to be toxic to plants via the atmosphere. Experiments performed with DEHP and DIDP did not reveal any effects upon plants, but due to experimental shortcomings they do not allow to conclude an absence of toxicity of DIDP to plants via the gas phase. No PNEC can be determined.

Terrestrial compartment

Short-term tests were performed with plants and earthworms. No effects were observed up to a concentration of 10,000 mg/kg dw. An assessment factor of 100 is applied instead of 1,000 as no LOECs could be determined, resulting in a $PNEC_{soil}$ of 100,000 µg/kg dw.

Secondary poisoning

The lowest overall NOAEL of 15 mg/kg bw/d has been determined in a 13-week repeated dose study with dogs. This corresponded to a food concentration of 500 mg/kg. Using an assessment factor of 10, a PNECoral of 50 mg/kg can be estimated for top predators.

3.3 RISK CHARACTERISATION

Aquatic compartment (including sediment and wastewater treatment plants)

The highest value estimated for a STP outlet is 20.75 mg/l. No PNEC could be derived, as no effects at the limit of water solubility could be observed. **Conclusion (ii)**.

No chemical toxic effects of DIDP towards fish, invertebrates or algae could be observed in any of the performed long-term tests. No NOECs could be derived. The assessment scheme proposed in the TGD can therefore not be used to derive a PNEC for the aquatic compartment. As furthermore, a two-generation study in fish exposed orally was performed, showing no impact on any populational parameter, it can tentatively be concluded that DIDP does not cause adverse chemical effects towards the aquatic ecosystem. **Conclusion (ii**).

Regarding the benthic compartment, long-term tests have been performed with vertebrates (moorfrog) and invertebrates (midge). No effects could be observed in any of the tests. No NOECs could be derived. It can therefore tentatively be concluded, that this compound does not cause adverse effects towards benthic organisms. **Conclusion (ii**).

Atmosphere

It is so far not possible to realise a biotic assessment in the same way as described for other compartments. No PNEC could be derived from the results available, as no dose-response relationship could be established. The absence of adverse effects in the test systems does not give rise for immediate concern though. **Conclusion (ii)**.

Terrestrial compartment

In **Table 3.3**, the ratios PEC/$PNEC_{soil}$ are shown. Local $PECs_{soil}$ for production sites have not been calculated as most producers dispose of their sewage sludge either through incineration or landfilling.

Table 3.3 PEC/PNEC ratios for agricultural soil

Life cycle step		$PEClocal_{soil}/PNEC_{soil}$
Processing in PVC *(highest release)*		≤ 0.16
Processing in non-PVC		≤ 0.08
Use in anti-corrosion paints	I *	≤ 0.05
	II*	negligible
Use in anti-fouling paints	II	≤ 0.03
Use in sealing compounds	I	≤ 0.05
Use in inks for textiles	I	≤ 0.05
	II	≤ 0.001

* formulation
** processing

As all calculated PEC/PNEC ratios are below 1, it can be concluded that there is no risk to soil dwelling organisms through DIDP. **Conclusion (ii)**.

Secondary poisoning

In **Table 3.4**, the PEC/PNEC ratios for top predators are presented.

Table 3.4 PEC/PNEC ratios for predators

Life cycle step		**PECbiota$_{aquatic}$ / PNEC$_{oral}$**	**PECbiota$_{soil}$ / PNEC$_{oral}$**
Production *(highest release)*		0.31	0.0022
Processing in PVC *(highest release)*		0.63	0.12
Processing in non-PVC polymers		0.39	0.062
Use in anti-corrosion paints	I*	0.29	0.04
	II*	0.13	0.0004
Use in anti-fouling paints	II	0.25	0.03
Use in sealing compounds	I	0.29	0.04
Use in inks for textiles	I	0.29	0.04
	II	0.13	0.001

* formulation
** processing

As for all scenarios PEC/PNEC ratios are below 1, it can be concluded that there is no risk towards top predators from DIDP. **Conclusion (ii)**.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Occupational exposure

Occupational exposure to DIDP may occur:

- by skin contact with pure DIDP, or mixtures (formulations) or end products containing it,
- by inhalation (vapours and aerosols).

Oral exposure is not considered to be a significant route of exposure under normal working practices.

Few countries have defined Occupational Exposure Limits for DINP. In the UK, the HSE (1997) indicates an occupational exposure standard (8-hour TWA) of 5 mg/m^3 for DIDP (CAS 26761-40-0). In Sweden, KEMI (1997) indicates a "level limit value" of 3 mg/m^3 and a "short-term value" of 5 mg/m^3 which apply to phthalates such as DIDP for which no specific-limit values have been defined.

Workers may be exposed to DIDP at different representative stages of its life cycle. The following exposure scenarios are considered:

1. manufacture of DIDP (reactor opening, drumming, pumping into tanks, cleaning, maintenance, etc.),
2. manufacture of products containing DIDP as a plasticiser or a solvent (adding, mixing, processing e.g. calendering, extruding, injection moulding, etc.)
3. use of end products containing DIDP (use of e.g. coatings, adhesives or inks).

In PVC formulations, the typical amount of DIDP is about 20 - 40% but may go up to 55%. In end products, the amount varies greatly from less than 1% to more than 50%.

Dermal exposure

In view of the very low absorption of DINP by the dermal route, a maximum dermal exposure of 5 mg/cm^2 is intentionally assumed for all scenarios. Actual levels of dermal exposure are much lower in most occupational circumstances.

Inhalation exposure

Inhalation occupational exposure is resumed in **Table 4.1**.

Table 4.1 Inhalation occupational exposure

Scenario	Estimated inhalation exposure level (mg/m^3 8-hour TWA)	
	Worst case	Typical
1- Production of DIDP	5	2
2- Manufacture of products containing DIDP	10	3
3- Use of end products containing DIDP	10	1.5

Due to the very low vapour pressure of DIDP, exposure by inhalation is in fact to air-borne particles (aerosols).

Consumer exposure

DIDP is a plasticiser used in several flexible PVC end products as cables and wires, sheets, film, wall- and roof covering, flooring, coatings and synthetic leather (car seats, home furniture), shoes and boots, outdoor and rainwear, car under-body coating. DIDP is also used in several non-PVC end products as paints, printing inks, rubbers, latex and adhesives. All of these products are available to consumers. However, DIDP is not available to consumers as such. Consumer exposure may also occur through food and drinking because of contamination from packaging and processing equipment containing DIDP.

DIDP had been used in toys in the past, so it may be considered as an alternative to other phthalates in the future, consequently it may be of value to consider the risks of such possibility.

The young children exposure to DIDP will be assessed in two ways:

- without the toy scenario, regarding the present situation,
- with the toy scenario, considering the foreseeable future use of DIDP as a substitute for other phthalates in toys.

Table 4.2 summarises the end products containing DIDP, the sources of exposure and the categories of consumers exposed.

Table 4.2 End products containing DIDP, sources of exposure and categories of consumers exposed

End-products/sources	Routes of exposure		
	Inhalation	Dermal exposure	Ingestion
Building materials and furniture	A-I-N	I-N	I-N
Toys and baby equipment	A-I-N	I-N	I-N
Car and public transport interiors	A-I-N	A-I-N	
Clothes	A-I-N	A-I-N	
Shoes	A-I-N	A-I	
Gloves	A-I-N	A	
Food and food related uses			A-I-N

A Adult
I Infants (6 months to 3 years old)
N Newborn babies (0 to 6 months old)

Human internal exposures were calculated taking into account the following bioavailability factors as well as differences in oral and inhalation uptake between children and adults:

- oral internal exposure: 50% for adults and 100% for newborns and infants,
- inhalation internal exposure: 75% for inhalation exposure in adults and 100% assumed for newborns and infants.

External and internal exposure for consumer are summarised in **Table 4.3**.

Table 4.3 External and internal exposure for consumers

Sources	External and internal exposure					
	Adults		New-borns 0 – 6 months old		Infants 6 months - 3 years old	
	External exposure	Internal exposure µg/kg/d	External exposure	Internal exposure µg/kg/d	External exposure	Internal exposure µg/kg/d
Building materials and furniture	20 µg/m³ *	4.2 a)	20 µg/m³ *	21.3 c)	20 µg/m³ *	21.3 c)
Car and public transport interiors	20 µg/m³ *	0.8 a)	20 µg/m³ *	1.9 c)	20 µg/m³ *	1.9 c)
Gloves, clothes and footwear		0.7	Not estimated			
Food and food-related uses	0.2 µg/kg/d	0.1 b)	2.4 µg/kg/d	2.4	2.3 µg/kg/d	2.3
Total without toys (*present situation*)		5.8		25.6		25.5
Toys and teething rings: oral exposure dermal exposure			200	200 c) 1	200 c)	200 c) 1
Total with toys (f*oreseeable situation*)				226.6		226.5

a) A bioavailability of 75% is considered for the inhalation route in adults
b) A bioavailability of 50% is considered for the oral route in adults
c) A bioavailability of 100% is considered for infants 6 months to 3 years old and for new-borns 0 to 6 months old by oral and respiratory routes
* Concentration in air

Humans exposed via the environment

Adults

Based on the regional concentrations, the total daily intake for humans is 0.002 mg/kg bw/d.

Infants (0.5 – 3 years old)

Based on the regional concentrations, the total daily intake for infants is 0.013 mg/kg bw/d.

Combined exposure

Internal exposure for adults, children and infants are presented in **Table 4.4**.

Table 4.4 Internal exposure for adults, children and infants

Sources of exposure	Internal exposure (mg/kg bw/d)		
	Adults	Infants without toys	Infants with toys
Occupational sources	1.10		
Consumer sources	0.01	0.01	0.23
Via the environment	0.01 a)	0.01 a)	0.17 b)
Total with occupational exposure **Total without occupational exposure**	**1.12** **0.02**	**0.02**	**0.40**

a) maximum daily intake of 0.027 derived from the use of DIDP in PVC, taking into account 50 % bioavailability for adults
b) maximum daily intake of 0.17 derived from the use of DIDP in PVC, taking into account 100 % bioavailability for infants.

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

The data available on toxicokinetic suggest that, via gastro-intestinal tract (GIT), absorption of DIDP decreases as dose increases (56% at the low dose of 0.1 mg/kg, 46% at the mid dose of 11.2 mg/kg and 17% at the high dose of 1,000 mg/kg) and seems to be of saturable mechanism; when dose increases, an increasing amount of unabsorbed compound is eliminated. Via the dermal route, the absorption is very low in rats. DIDP showed a very slow excretion, reflecting a slow dermal uptake process. The maximum percentage of absorption may be estimated 4% of applied dose in 7 days by analogy with DINP. In humans, skin absorption is still lower than in rat as indicated by *in vitro* comparative studies. Inhaled DIDP aerosol seems readily absorbed, thus a 75 % bioavailability seems realistic. In tissues, DIDP is mainly recovered in GIT, liver, kidneys, by the oral or inhalation route, whereas following dermal exposure, muscle and adipose tissues contain most of the dose remaining in the body. Only metabolites of DIDP (the oxidative monoester derivative and phthalic acid) are excreted in urine. In feces, the monoester oxidative derivative, MIDP (monoisodecyl phthalate) as well as DIDP were detected. DIDP is rapidly eliminated and not accumulated in tissues. By the oral and inhalation routes, excretion is shared between urine and faeces. By dermal exposure, only faecal elimination was indicated. In addition, results from a two-generation study suggest a possible transfer of DIDP through the milk when dams are exposed by the oral route.

Acute toxicity

Upon single exposure, DIDP has a low acute toxicity by all routes of administration.

Irritation

Human or animal data suggest no potential irritant effects on skin, eyes or respiratory system.

Sensitisation

There is no evidence for skin or respiratory sensitisation.

Repeated dose toxicity

The liver was identified as a target organ as a result of oral repeated exposure. In rodents, increases in liver weight were accompanied by biochemical evidence of peroxisomal proliferation; thus, a NOAEL of 60 mg/kg/d was identified in rats from a standard 90-day study. Findings in dogs were qualitatively consistent (increases in liver weight and swollen and vacuolated hepatocytes); a NOAEL of 15 mg/kg/d was derived from a 13-week oral dog study, in spite of the large limitations of this study.

Increases in kidney weights are also observed in repeated dose toxicity tests but in a non-consistent way and with no concurrent histopathological changes. Renal damages are only observed in a two-generation study (about 12 weeks) from 100 - 200 mg/kg/d, but only in male rats; a specific male rat effect is generally assumed.

In an inhalation study, there was no systemic effect observed and toxicity was limited to local inflammatory changes in the lung.

Mutagenicity

DIDP is not mutagenic *in vitro* in bacterial mutation assays (with and without metabolic activation) and is negative in a mouse lymphoma assay. It is not clastogenic in a mouse micronucleus assay *in vivo*. This indicates that DIDP is a non-genotoxic agent.

Carcinogenicity

Regarding carcinogenicity, cell transformation tests were conducted on DIDP. One positive result obtained is in accordance with those obtained with well-known peroxisome proliferators. No carcinogenicity long-term study is available for DIDP but an increase in incidence of hepatocellular tumours in rats related to peroxisome proliferation might be anticipated, in regard with the increased incidence in tumour liver cells observed with DEHP and DINP in carcinogenicity studies. Indeed, it is now well-accepted that peroxisome proliferation is specific to rodents. It has been established that peroxisome proliferators exhibit their pleiotropic effects due to activation of PPARα (peroxisome proliferator-activated receptor α) and that PPARα is expressed only at low level in humans, explaining the absence of significant response in humans to the action of peroxisome proliferators. Thus, there is no concern for a potential carcinogenic effect in humans through such a mechanism.

Toxicity for reproduction

Regarding toxicity for reproduction, in 42-44 day year old (pubertal) or adult rats there is no indication of organ reproductive effects evidenced by histological observation in repeated dose toxicity studies and a two-generation study. In this two-generation study, a decrease in mean percent normal sperm was observed but of low incidence and only in P1 generation. In pups (F1, F2 and in the cross fostering satellite group) decreases in testes weight and cryptorchidism in F2 high-dose offspring were observed, likely due to the low body weight, since no histopathological damages were observed in adult testes. There were no changes in reproductive indices. From those assays, no adverse effects on fertility may be anticipated.

Regarding developmental effects, treatment of dams from gd 6-15 did not cause structural malformations but consistently demonstrated skeletal variations (increased fœtal cervical and lumbar ribs) at 1,000 mg/kg/d concurrently with slight signs of maternal toxicity and lead to a NOAEL of 500 mg/kg/d; in a two-generation rat study, body weight decrease was observed in offspring partly related to lactation at the highest dose of 0.8% and leads to a NOAEL of 0.4% (253 to 761 mg/kg/d seeing that received doses are widely dependent on the period considered).

Developmental toxicity was observed consistently in the two-generation studies, where decrease in survival indices leads to a NOAEL of 0.06% (33 mg/kg/d DIDP).

A prenatal exposure study in mice conducted at 9,650 mg/kg/d does not affect pregnancy outcome, however, as this test was drawn for screening purpose, it is insufficient to conclude to an absence of effect.

DIDP is devoid of estrogenic activity *in vitro*, it shows no ability of binding to rodent or human estrogen receptors or to induce estrogen receptors-mediated gene expression. *In vivo* assays demonstrated that DIDP does not increase uterine wet weight or does not give rise to vaginal epithelial cell cornification. In a two-generation study, developmental landmarks (anogenital distance, nipple retention and preputial separation) are not impaired; this suggests a lack of anti-androgenic activities.

4.1.3 Risk characterisation

Repeated dose toxicity (RDT) and reproductive effects are considered to be the critical endpoints in the risk assessment of DIDP.

Workers

For the dermal route, the worst case for external skin exposure is considered to occur when 5 mg/cm^2 of pure DIDP is applied during 8 hours on a skin surface of 840 cm^2 (for both hands), then, for worst-case situations, it is proposed to take a maximum dermal intake of 2.4 mg/day equivalent to 0.03 mg/kg/day for a 70-kg man. For the inhalation route, the corresponding internal doses are calculated assuming 10 m^3 of air inhaled in an 8-hour working day by a 70-kg worker and a 75% pulmonary absorption rate. The MOSs have to be determined for route-specific as well as combined inhalation and dermal exposure. As internal exposure by dermal route is very low, much lower than by inhalation route, the most significant contribution to the conclusions is via inhalation.

Considering the estimated combined internal exposure and comparing the NOAELs (15 mg/kg/d in dogs and 60 mg/kg/d in rats for hepatic effects), the MOSs have been calculated. For the occupational exposure, these MOSs are considered sufficient since the NOAEL was based on very slight effects (increase of relative liver weights in female rats at the higher dose). For offspring survival, considering the estimated combined internal exposure and comparing with the NOAELs of 33 mg/kg/d (slight decrease of survival indices in the F2 generation at higher doses), the MOSs have been calculated and are considered quite sufficient for the occupational exposure. For developmental effects, the MOSs have also been calculated, considering the estimated combined internal exposure and the relevant NOAEL of 500 mg/kg/d (skeletal variations in developmental rat studies) and the NOAEL of 263 mg/kg/d (decrease body weight in rat); for both effects, the MOSs are considered sufficient for the occupational exposure.

Conclusion (ii).

Consumers

As DIDP is present in several end products available to consumers, especially those in soft-PVC, consumer exposure can occur from various sources by different routes (inhalation, dermal, oral) in different situations.

Scenarios were built for three sub-populations:

Adults and children 3-15 years old

The MOSs are calculated for multiple exposure pathways and include exposure from the four scenarios (Building materials and furniture / Clothes, gloves and footwears / Car and public transport interior / Food and food-related uses). For all endpoints the MOSs are considered sufficient to protect adult consumers. **Conclusion (ii)**.

Infants 6 months to 3 years old

Four exposure scenarios are considered as important for infants and newborns: Toys and baby equipment (foreseeable situation) / Building material and furniture / Food and food-related uses / Car and public transport interior. The MOSs are calculated in two ways: with or without toys exposure.

For repeated dose toxicity, the MOSs are considered sufficient to protect infants, except for the scenario with toys, based on the repeated dose toxicity dog study. So, in case DIDP should be a substitute for other phthalates in toys in the future, the MOS of 33, derived from hepatic toxicity in dog, would not be considered sufficient to protect infants. **Conclusion (iii)**.

Pertaining to reduced offspring survival (trans-generational effect observed in a two-generation rat study), in any case, owing to the uncertainty on the applicability of the NOAEL (16.5 mg/kg bw/d in rats) and the significance of the MOSs (635 and 73, respectively without and with toys), no formal conclusion could be drawn.

Newborns 0 to 6 months old

Exposure scenarios are the same for newborns and infants. The MOSs are calculated in two ways: with and without toys taking into account the whole internal exposure pathways for those specific consumers.

For repeated dose toxicity, the MOSs are considered sufficient to protect newborns, except for the scenario with toys, based on the repeated dose toxicity dog study. So, in case DIDP should be a substitute for other phthalates in toys in the future, the MOS of 33, derived from hepatic toxicity in dogs, would not be considered sufficient to protect newborns. **Conclusion (iii)**.

Pertaining to reduced offspring survival (trans-generational effect observed in a two-generation rat study), in any case, owing to the uncertainty on the applicability of the NOAEL (16.5 mg/kg bw/d in rats) and the significance of the MOSs (635 and 73, respectively without and with toys), no formal conclusion could be drawn.

Humans exposed via the environment

The exposure assessment has shown that the main route of intake is by the oral route.

For repeated dose toxicity, in adults and infants 3-15 years old, the MOSs have been calculated for the lowest NOAELs (the internal NOAEL for hepatic effects in rats being set at 30 mg/kg bw/d and the internal NOAEL for hepatic effects in dogs being set at 7.5 mg/kg bw/d). The estimated MOSs are considered sufficient for exposure of this population via the environment. In infants 0.5-3 years old, as the bioavailability of DIDP in children is assumed to be higher than in adults, an internal dose corresponding to 100% of the external dose will be used. The MOSs have been calculated for the lowest NOAELs (the internal NOAEL for hepatic effects in rats being set at 30 mg/kg bw/d and the internal NOAEL for hepatic effects in dogs being set at 7.5 mg/kg bw/d). The estimated MOSs are considered sufficient for exposure of infants via the environment. **Conclusion (ii)**.

For fertility, in adults and children 3-15 years old, the estimated MOSs for offspring survival are considered sufficient for exposure of adults via the environment. Pertaining to reduced offspring survival (trans-generational effect observed in a two-generation rat study), in any case, owing to the uncertainty on the applicability of the NOAEL (16.5 mg/kg bw/d) and the significance of the MOS (93), no formal conclusion could be drawn.

For developmental toxicity, considering the relevant NOAELs of 500 mg/kg/d (skeletal variations) and 253 mg/kg/d (decrease in body weight), the MOSs can be calculated and are considered sufficient to protect adults. **Conclusion (ii)**.

Combined exposure

As combined exposure of adults is almost exclusively related to occupational exposure, the MOSs are considered sufficient for adults. For children 3-15 years old, the MOSs are also considered sufficient. **Conclusion (ii)**.

As combined infant exposure without toys is almost exclusively related to environmental exposure, the MOSs are considered to protect infants 0.5-3 years old. For repeated dose toxicity, the MOSs are considered sufficient to protect infants, except for the scenario with toys, based on the repeated dose toxicity dog study. So, in case DIDP should be a substitute for other phthalates in toys in the future, MOS of 18.8, derived from hepatic toxicity in dogs, would not be considered sufficient to protect infants. **Conclusion (iii)**.

Pertaining to reduced offspring survival (trans-generational effect observed in a two-generation rat study), in any case, owing to the uncertainty on the applicability of the NOAEL (16.5 mg/kg bw/d) and the significance of the MOSs (83 and 41, respectively without and with toys), no formal conclusion could be drawn.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

No specific exposure information is available on the exposure assessment for workers.

Concerning the effect assessment, the properties of explosivity, flammability and oxidisation are not considered to pose a hazard. **Conclusion (ii)**.

5 RESULTS

5.1 ENVIRONMENT

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

The production and use of DIDP in PVC, other polymers, paints, sealing compounds and textile inks is unlikely to pose a risk to the environment. In addition, risks to the function of sewage treatment plants and the atmosphere are expected to be very low for both production and all uses.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

The production and use of DIDP in PVC, other polymers, inks, adhesives and coatings is not considered of concern for occupational exposure (inhalation and skin contact).

Consumers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies in case DIDP should be used as a substitute for other phthalates in toys because of concerns for hepatic toxicity as a consequence of repeated exposure of infants and newborn babies arising mainly by the oral route from mouthing and sucking toys and baby equipment.

Pertaining to reduced offspring survival, due to the uncertainty related to the relevance of this endpoint for new-borns and infants and to the lack of experience in this particular field of trans-generational effect, no formal conclusion could be drawn.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

The end products containing DIDP (clothes, building materials) and the sources of exposure (car and public transport interiors, food and food packaging) are unlikely to pose a risk for consumers (adults, infants and new-borns) following inhalation, skin contact and ingestion.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

The indirect exposure via the environment is unlikely to pose a risk to humans following the main route of exposure, the oral route.

Combined exposure

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion applies in case DIDP should be used as a substitute for other phthalates in toys because of concerns for hepatic toxicity as a consequence of repeated exposure of infants.

Pertaining to reduced offspring survival, due to the uncertainty related to the relevance of this end point for infants and to the lack of experience in this particular field of trans-generational effect, no formal conclusion could be drawn.

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

As combined exposure of adults is almost exclusively related to occupational exposure, the overall assessment indicates no concern for adults. For infants, combined exposure, which is mainly related to exposure via the environment, is not considered of concern.

5.2.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Concerning the effect assessment of DIDP, the properties of explosivity, flammability and oxidisation are not considered to pose a hazard.