EUROPEAN COMMISSION

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1,2-BENZENEDICARBOXYLIC ACID, DI-C8-10-BRANCHED ALKYL ESTERS, C9-RICH

and

DI-"ISONONYL" PHTHALATE

(DINP)

CAS Nos: 68515-48-0 and 28553-12-0

EINECS Nos: 271-090-9 and 249-079-5

Summary Risk Assessment Report

2003 **Special Publication I.03.101**

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2003

France

The French rapporteur for the risk evaluation of 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich and di-"isononyl" phthalate is the Ministry of the Environment with the Ministry of Health and the Ministry of Work.

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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-C8-10-branched alkyl esters, C9-rich and di-"isononyl" 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

Explanatory note: 3 DINPs, one risk assessment report

There are 3 different substances attributed to the names 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich or di-"isononyl" phthalate (DINP). DINP 1 (CAS 68515-48-0) is manufactured by the "Polygas" process. DINP 2 (CAS 28553-12-0) is *n*-butene based. DINP 3 (also CAS 28552-12-0) is *n*- & iso-butene based. Chemical structures consequently differ. Thus, these 3 DINPs could have different physico-chemical and toxicological properties, and should be dealt with separately.

The manufacture of DINP 3 was stopped in 1995. A risk assessment for this substance is therefore not justified. Relevant data were however used in this report when it helps to better understand some aspects of physico-chemical or toxicological properties.

Before 1995, the 3 DINPs have been submitted to different physico-chemical and toxicological tests, but detailed sample compositions were not always available and references sometimes vague (such as "DINP") or provided only under coded references, rarely traceable to well-defined samples. Even when a CAS number was indicated for the sample being tested, sample composition may not be warranted, since DINP 2 and DINP 3, although different, were attributed the same CAS number. It has also to be noted that some DINPs seem to have been produced by specific processes and may be still different although having the same CAS number (e.g. Hoechst's Genomoll 150, CAS 28553-12-0, which contains di-(3,5,5-trimethylhexyl)-phthalate as a main constituent).

Thirdly, a "pure" DINP sample is a rather complex mixture, and its physico-chemical properties may be more or less well characterised. Moreover, the 3 DINPs may share common constituents. They cannot be differentiated through their physico-chemical properties.

It is concluded that only one risk assessment report may usefully be presented.

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TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 68515-48-0 and 28553-12-0
EINECS Number: 271-090-9 and 249-079-5
IUPAC Name: 1,2-Benzenedicarboxylic acid, di-C8-10 branched alkyl esters, C_9 rich and di-"isononyl" phthalate
Molecular weight: Average 420.6
Molecular formula: $C_{8+2x}H_{6+4x}O_4$ with x = 8 to 10
(x = 9 as main constituent), average $C_{26}H_{42}O_4$

1.2 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value
Melting point	ca. -50°C
Boiling point	> 400°C
Density	ca. 0.975 at 20°C
Vapour pressure	$6 \cdot 10^{-5}$ Pa at 20°C
Water solubility	0.6 µg/l at 20°C
Henry's law constant	41.4 Pa · m^3/mol
Log Kow	8.8
Flash point	> 200°C
Autoflammability	ca. 380°C
Viscosity	ca. 100-150 mPa · s

1.3 CLASSIFICATION

No classification.

2 GENERAL INFORMATION ON EXPOSURE

There are currently four producers of DINP in the EU. The estimated consumption volume in 1994 is ca. 107,200 t/a. An increase of the consumption of DINP is to be expected over the following years. Approximately 95% of DINP are used in PVC as a plasticiser. The remaining 5% are used in non-PVC applications. More than half of the DINP used in non-PVC applications involves polymer-related uses (e.g. rubbers). The remaining DINP is used in non-polymer applications including inks, adhesives and sealants, paints and lacquers.

For the estimation of the releases to the environment through articles containing DINP, 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 DINP in different articles and their respective lifetimes

Application	DINP [t/a]	Technical lifetime
Indoor application		
Wires & cables	14,510	30
Floor	10,658	20
Outdoor application		
Roofing material	230	20
Roofing (coil coating)	1,150	10
Wires & cables	14,510	30
Coated fabric	4,850	10
Hoses & Profiles	1,380	10
Car under-coating	7,714	14
Shoe soles	8,313	5
Sealings	915	20
Paints & lacquers	915	7

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

As DINP 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 DINP relevant for the exposure assessment are:

- no hydrolysis in water,
- readily degradable;(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 DINP),
- an estimated atmospheric half-life of 0.7 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 800 to 4,000) have been reported with certain freshwater organisms.

Based on the model SIMPLETREAT, it is estimated that in sewage treatment plants, 82% of any discharged DINP will be adsorbed on to sludge, 10% will be degraded and 1% will be stripped to air, with the remaining 7% 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 DINP in inks, adhesives, sealants, paints and lacquers, 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	41	29	-	-	-	-
Distribution	8.5	0.94	-	-	-	-
Processing in PVC	40.2	4.4			40.4	4.74
Processing in non-PVC polymers	4.6	0.51			4.6	0.51

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 as an additive in adhesives, glues and sealing compounds						
Formulation	8.2	0.91	-	-	2.1	0.23
Application	-	-	-	-	0.08	0.01
Use as an additive in inks for paper						
Formulation	8.2	0.91	-	-	2.1	0.23
Application	0.4	0.045	-	-	-	-
Use as an additive in paints						
Formulation	8.2	0.91	-	-	2.1	0.23
Application	0.8	0.09	-	-	-	-
Exterior and interior use of DINP-containing PVC-products	212.7	23.6	179.6	19.9	37.6	4.2
Use of DINP-containing non-PVC products	5.8	0.64	4.87	0.54	1.0	0.11
Applied sealings containing DINP	-	-	4.57	0.51	0.08	0.01
Paper recycling	5	0.55	-	-	-	-
Applied paints containing DINP	-	-	16.1	1.8	0.3	0.03
Disposal of end products	-	-	710	78.9	29.9	3.4
Total	**343**	**62.5**	**915**	**102**	**120**	**13.5**

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 DINP, 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 DINP

Life cycle step		PEClocal$_{water}$ [µg/l]	PEClocal$_{sed}$ [µg/kg dw]	PEClocal$_{soil}$ [µg/kg dw]	PECbiota$_{aquatic}$ [µg/kg ww]	PECbiota$_{soil}$ [µg/kg ww]
Production (highest release)		2.2	2,000	-	4.62	0.01
Processing in PVC (highest release)		9.7	150,000	10,900	17.9	4.1
Processing in non-PVC		3.4	47,000	3,300	7.6	1.2
Use in adhesives, glues and sealing compounds	I *	8.1	133,600	8,950	14.9	3.35
Use in inks for paper	I	8.1	133,600	8,970	14.9	3.35
	II **	1.3	12,300	740	2.93	0.28
Use in paints	I	8.1	133,600	8,960	14.9	3.35
	II	1.4	14,000	880	3.1	0.33
Paper recycling		1.2	10,700	660	3.49	0.25

* 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. Available long-term test results with fish exposed via the water phase were considered to be invalid. Furthermore, 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 DINP.

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 DINP up to concentrations of 1,000 mg/kg dw was not affected. As it could be concluded that DINP 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 DINP on fish.

Atmosphere

Some phthalates, especially dibutylphthalate (DBP) have shown to be toxic to plants via the atmosphere. No results are available with DINP. 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 DINP to plants via the gas phase. No PNEC can be determined.

Terrestrial compartment

Short-term tests were performed with plants and earthworms. Long-term test results are available with plants and microorganisms. A result regarding inhibition of germination in a short-term test was not confirmed in a corresponding long-term test. The highest tested concentrations range from 1,500 to 10,000 mg/kg dw. The NOEC of 1,500 mg/kg will therefore be used with an assessment factor of 50 resulting in a PNEC of 30,000 µg/kg dw.

Secondary poisoning

The lowest overall NOAEL of 88 mg/kg bw/d has been determined in a two-year repeated dose study with rats. This corresponded to a food concentration of 1,500 mg/kg. Using an assessment factor of 10, a PNECoral of 150 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 3.4 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 DINP 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 DINP does not cause adverse chemical effects towards the aquatic ecosystem. **Conclusion (ii**).

Regarding the benthic compartment, a long-term test has been performed with vertebrates (moorfrog) and a read-across from long-term tests performed with DEHP and DIDP on invertebrates (midge) can be performed. In none of the test systems could any effects be observed. No NOECs could be derived. The equilibrium partitioning model described in the TGD cannot be used to estimate a $PNEC_{sediment}$ as no aquatic PNEC could be derived due to the lack of identified adverse effects. It can therefore tentatively be concluded, that this compound has no 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 results are available with DINP. No PNEC could be derived from the results available for analogues e.g. DIDP, 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)*		0.30
Processing in non-PVC *(highest release)*		0.11
Use in adhesives, glues and sealing compounds	I *	0.30
Use in inks for paper	I	0.30
	II **	0.02
Use in paints	I	0.30
	II	0.03
Paper recycling		0.02

* formulation
** processing

As all calculated PEC/PNEC ratios are below 1, it can be concluded that there is no risk to terrestrial organisms through DINP. **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)		0.03	0.00007
Processing in PVC (highest release)		0.12	0.03
Processing in non-PVC polymers		0.05	0.01
Use in adhesives, glues and sealing compounds	I *	0.10	0.02
Use in printing inks	I	0.10	0.02
	II **	0.03	0.0003
Use in paints	I	0.10	0.02
	II	0.02	0.002
Paper recycling		0.02	0.0002

* formulation
** processing

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

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

Occupational exposure

Occupational exposure to DINP may occur:

- by skin contact with pure DINP, 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 DINP 2 (CAS 28553-12-0). 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 DINP for which no specific-limit values have been defined.

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

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

In PVC formulations, the typical amount of DINP 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 DINP	5	2
2- Manufacture of products containing DINP	10	3
3- Use of end products containing DINP	10	1.5

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

Consumer exposure

The main difficulty in assessing the level of consumer exposure to DINP is the ubiquity of this compound. As DINP is not chemically bound to PVC, it can be released during the entire cycle of life of end products that are used by consumers. These end products are building materials (cables, floor covering, paints, etc.), car undercoating, clothes, gloves, shoes and boots, etc. DINP has also been found in toys and child care articles. But DINP 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 DINP.

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

Table 4.2 End products containing DINP, 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
Car and public transport interior	A-I-N	A-I-N	
Clothes	A-I-N	A-I-N	
Shoes	A-I-N	A-I	
Gloves	A-I-N	A	
Toys and baby equipment	A-I-N	I-N	I-N
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	40 µg/m³ *	8.3 a)	40 µg/m³ *	42.6 c)	40 µg/m³ *	42.6 c)
Car and public transport interiors	40 µg/m³ *	1.7 a)	40 µg/m³ *	3.9 c)	40 µg/m³ *	3.9 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		**10.8**		**48.9**		**48.8**
Toys and teething rings: oral exposure dermal exposure			200	200 c) 1	200 c)	200 c) 1
Total with toys				**249.9**		**249.8**

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

The estimated maximum total daily intake of 0.028 mg/kg bw/d will therefore also be used in the risk characterisation.

Infants (0.5-3 years old)

The estimated maximum total daily intake of 0.156 mg/kg bw/d will therefore also be used in the risk characterisation.

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 (>16 years old)	Children (3-15 years old)	Infants (0.5-3 years old)
Occupational sources	1.10		
Consumer sources (with toys for infants)	0.01	0.01	0.25
Via the environment	0.01	0.01	0.16
Total	**1.12**	**0.02**	**0.41**

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

The data available on toxicokinetic suggest that, via gastro-intestinal tract (GIT), absorption of DINP decreases as dose increases (49% at the low dose of 50 mg/kg and 39% at the high dose of 500 mg/kg eliminated in urine); in addition, absorption of the substance seems to be a saturable mechanism. Dermal absorption is slow in rats. The maximum percentage of the applied substance being absorbed in 7 days is less than 4%. In humans skin absorption is still lower than in rat as indicated by *in vitro* comparative studies. Via inhalation, a bioavailability of 75% may be assumed by analogy with DIDP. In tissues, DINP is mainly recovered in GIT, liver and kidney by oral route whereas following dermal exposure, liver, muscle and adipose tissues contain most of the dose remaining in the body. DINP metabolites were excreted in urine and to a lesser extent in feces. DINP was de-esterified to the monoester which was further metabolised by side-chain oxidation of the ester group or by hydrolysis to phthalic acid. Repeated dosing caused no accumulation of DINP and/or its metabolites in blood and tissue, but resulted in increased formation and elimination of the monoester-oxidation products. DINP is rapidly eliminated. By the oral and dermal routes, excretion is shared between urine and feces. By dermal exposure, biliary excretion is shown.

Acute toxicity

Upon single exposure, DINP 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.

Repeated dose toxicity

The liver is a target for chronic toxicity and a NOAEL of 88 mg/kg/d was assumed for liver effects based on hepatic biochemical changes (increased aspartate-aminotransferase, AST and alanine-aminotransferase, ALT) and on increases of liver weight with histopathological findings. Repeated-dose studies performed to assess the peroxisomal proliferation potential of DINP, reveal biochemical evidence of peroxisome proliferation in rodents. In contrast, there was no evidence of peroxisome proliferation in marmosets or in cynomolgus monkeys; in humans as well, there is no significant response to peroxisome proliferators.

For kidney effects, a NOAEL of 88 mg/kg/d was determined, based on increased kidney weights. Histologically, there was an increase in frequency/severity of chronic progressive nephropathy at quite low doses, but specifically in males. Histological features are consistent with the specific male rat nephropathy irrelevant to humans, namely alpha 2u globulin nephropathy. It was demonstrated, by immunohistochemical techniques, that exposure to DINP results in a dose dependant alpha 2u globulin accumulation in male rat kidneys and is likely the mechanism for kidney tumours seen only in male rats administered high dietary levels of DINP. In mice, there was also progressive nephropathy observed at very high doses.

Mutagenicity

DINP is not mutagenic *in vitro* in bacterial mutation assays or mammalian gene mutation assay (with and without metabolic activation) and is not clastogenic in one cytogenetic assay *in vitro* on CHO cells and in one *in vivo* assay on bone marrow cell of Fisher 344 rats. This suggests that DINP is not genotoxic.

Carcinogenicity

In chronic/carcinogenicity studies, DINP was found to induce significant excess of liver neoplasia in rats and mice after oral administration. This is consistent with a peroxisome proliferation mode of action for hepatic tumour induction specific in rodent. 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 to the action of peroxisome proliferators, thus, there is no concern for a potential carcinogenic effect in humans.

Regarding MNCL (mononuclear cell leukemia), a clearly increased incidence is observed in the two studies conducted with Fisher rats. However, MNCL, a common neoplasm in the Fischer 344 rats, was categorised by IARC as "an unclassified leukemia with no known human counterpart" and substances which increase MNCL frequency as "not classifiable as to carcinogenicity in humans". Pertaining to kidney tumours, the species and sex-specific alpha 2u globulin mechanism likely responsible for kidney tumours seen in male rats is not considered as relevant to humans.

Toxicity for reproduction

Regarding fertility, no adverse effects are anticipated in adult rats on reproductive organs, in repeated dose toxicity and in one-generation studies. In mice, a very high dose (5,770 mg/kg/d) leads to decrease in testicular weight with abnormal/immature sperm forms and uterus/ovaries atrophy in the 13-week study. In the 104-week chronic study, a NOAEL of 1,500 ppm (276 mg/kg/d) can be assumed for testicular effects, based on decrease in testicular weight (relative and absolute) observed from 742 mg/kg/d. Testicular lesions were not observed in a 13-week gavage study in adult marmosets well as in a 2-week gavage study in prepubertal cynomolgus monkeys. In a two-generation study, no changes in reproductive indices are observed.

In the developmental studies, visceral (dilated renal pelvis and hydroureter) and skeletal variations (increases in lumbar and cervical ribs) were significantly increased on a litter basis at 1,000 mg/kg/d, leading to a NOAEL of 500 mg/kg/d. In addition, a decrease of mean offspring body weight was observed following parental administration of DINP in the one and two-generation studies from the lowest dose tested (LOAEL of 159 mg/kg/d). In a two-generation study, parental toxicity was limited to lower mean body weight and hepatic changes.

In regard with offspring survival in rats, a decrease of life birth and survival indices was observed in a one-generation range-finding study at doses higher than 1,000 mg/kg/d.

DINP is devoid of estrogenic activity *in vitro*, it does not show ability of binding to rodent or human estrogen receptors or to induce estrogen receptors-mediated gene expression. *In vivo* assays demonstrated that DINP does not increase uterine wet weight or does not give rise to vaginal epithelial cell cornification. However, a recent study in rats (perinatal exposure) indicated that infants male displayed female like areolas/nipples and that incidence of reproductive malformation was slightly but significantly increased (7.7% versus 91% with DEHP).

4.1.3 Risk characterisation

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

Workers

For the dermal route, the worst case for external skin exposure is considered to occur when 5 mg/cm^2 of pure DINP 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 are inhaled in a 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 the 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 of 88 mg/kg/d for hepatic effects and of 88 mg/kg/d for kidney effects in rats, the MOSs have been calculated. For the occupational exposure, these MOSs can be considered acceptable. For fertility (testicular effects) and offspring survival, considering the estimated combined internal exposure and comparing the NOAELs of 622 mg/kg/d (decrease of live birth and survival indices in the one-generation rat study) and of 276 mg/kg/d (testicular effects in mice in a 104-week study), 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 LOAEL of 159 mg/kg/d (decrease offspring body weight in the 2-generation rat study); for both effects, the MOSs are considered sufficient for the occupational exposure. **Conclusion (ii).**

Consumers

As DINP 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 subpopulations:

Adults and children 3-15 years old

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

Infants 6 months to 3 years old

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

For all endpoints, the MOSs are considered sufficient for infants.

Pertaining to reduced offspring survival (observed in the one-generation rat study), in any case, owing to the uncertainty related to the relevance of this endpoint for infants, no formal

conclusion could be drawn. Nevertheless, considering the NOAEL of 311 mg/kg bw/d, the MOSs (6,347 and 1,244, respectively without and with toys) would be sufficient to protect infants.

Conclusion (ii).

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 all endpoints, the MOSs are considered sufficient for newborns.

Pertaining to reduced offspring survival (observed in the one-generation rat study), in any case, owing to the uncertainty related to the relevance of this endpoint for newborns, no formal conclusion could be drawn. Nevertheless, considering the NOAEL of 311 mg/kg bw/d, the MOSs (6,347 and 1,244, respectively without and with toys) would be sufficient to protect newborns.

Conclusion (ii).

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 children 3-15 years old, the highest estimated total daily intake is 0.028 mg/kg bw/d, corresponding to an internal exposure of 0.014 mg/kg bw/d. The estimated MOS is considered sufficient for the exposure of this population via the environment. In infants (0.5-3 years old), the highest estimated total daily intake is 0.156 mg/kg bw/d, corresponding to an internal dose of 0.156 mg/kg bw/d. The estimated MOS is considered sufficient for the exposure of this sub-population via the environment, especially as the risk characterisation is specific for young children and not the overall population.

For reproductive toxicity, in adults and children 3-15 years old, the calculated MOSs for the lowest NOAELs determined for fertility and developmental effects, are considered sufficient for the exposure of this population via the environment. In infants (0.5-3 years old), a MOS of 885 was calculated for the lowest NOAELs determined for fertility (testicular effects). Moreover, reduced offspring survival, observed in the one-generation rat study**,** might be taken into account for infants and considering the internal exposure of 0.156 mg/kg bw/d and the internal NOAEL of 311 mg/kg bw/d in rats, the MOS would be 1,994. These MOSs are considered sufficient for the exposure of infants via the environment.

Conclusion (ii).

Combined exposure

As combined exposure of adults is almost exclusively related to occupational exposure, the MOSs indicate no reason for concern. For children 3-15 years, the MOSs also indicate no reason for concern. **Conclusion (ii)**.

Pertaining to reduced offspring survival (observed in the one-generation rat study), owing to the uncertainty related to the relevance of this endpoint for infants, 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 DINP in PVC, other polymers, inks, adhesives, sealants and paints 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 DINP in PVC, other polymers, inks, adhesives and coatings is not considered of concern for occupational exposure (inhalation and skin contact).

Consumers

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 DINP (clothes, building materials, toys and baby equipment) 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 newborns) 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 (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 from toys and 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 DINP, the properties of explosivity, flammability and oxidisation are not considered to pose a hazard.