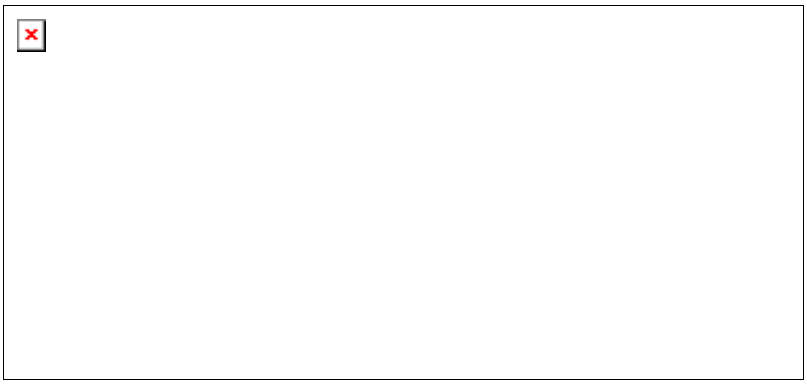

Printing Date 2010-01-06 07:50:50 CET

Restriction of specific regulatory purposes

EU: REACH, other:

Confidentiality

Name	53306-54-0_master_bis(2-propylheptyl) phthalate (IUC4 DSN 4)
Legal entity owner	BASF SE / Ludwigshafen am Rhein / Germany

Substance: 53306-54-0_master_bis(2-propylheptyl) phthalate (IUC4 DSN 4)

UUID	IUC4-f40e8b0f-7260-3e05-ad06-e97e663f427f
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-12-28 17:39:23 CET
Remarks	Created endpoint study record 7.1 Toxicokinetics, metabolism and distribution

0 Related Information
0.1 Templates
0.2 Categories
0.3 Mixtures
1 General Information
1.1 Identification
Substance identification

Chemical name 53306-54-0_master_bis(2-propylheptyl) phthalate (IUC4 DSN 4)

EU: REACH

Legal entity BASF SE / Ludwigshafen am Rhein / Germany

EU: REACH

Role in the supply chain

EU: REACH

Role: ( ) Manufacturer ( ) Importer ( ) Only representative ( ) Downstream user

Reference substance

Reference substance bis(2-propylheptyl) phthalate / bis(2-propylheptyl) phthalate / 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester / 53306-54-0

EC number	EC name
258-469-4	bis(2-propylheptyl) phthalate
CAS number	**CAS name**
53306-54-0	1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester

IUPAC name

bis(2-propylheptyl) phthalate

Type of substance

Composition other: Existing Chemical

Origin organic

Trade names

EU: REACH

Name bis(2-propylheptyl)phthalate

Name Bis(2-propylheptyl)phthalat

Name Di-2-propylheptyl phthalate

Name Di-2-propylheptylphthalat

Name DPHP

Name Palatinol 10-P

Name Phthalic acid, bis(2-propylheptyl) ester

Contact person

Person flags **EU: REACH**

1.2 Composition

2 Classification and Labelling

2.1 GHS

Classification and Labelling according to GHS

EU: REACH

General information

Name	bis(2-propylheptyl)phtalate
	(X) Not classified
Implementation	EU

Classification

Physical hazards

	Hazard statement	Reason for no classification
Explosives		
Flammable gases		
Flammable aerosols		
Oxidizing gases		
Gases under pressure		
Flammable liquids		
Flammable solids		
Self-reactive substances and mixtures		
Pyrophoric liquids		
Pyrophoric solids		
Self heating substances and mixtures		
Substances and mixtures which in contact with water emits flammable gases		
Oxidising liquids		
Oxidising solids		
Organic peroxides		

Substance and mixtures corrosive to metals	

Health hazards

	Hazard statement	Reason for no classification
Acute toxicity - oral		conclusive but not sufficient for classification
Acute toxicity - dermal		conclusive but not sufficient for classification
Acute toxicity - inhalation		
Skin corrosion/irritation		conclusive but not sufficient for classification
Serious damage/ eye irritation		conclusive but not sufficient for classification
Respiratory sensitization		
Skin sensitization		conclusive but not sufficient for classification
Aspiration hazard		

Germ cell mutagenicity

Hazard statement	Reason for no classification

Carcinogenicity

Hazard statement	Reason for no classification

	Hazard statement	Reason for no classification
Reproductive toxicity		conclusive but not sufficient for classification
Specific effect		
Route of exposure		
Effects on or via lactation		conclusive but not sufficient for classification

Specific target organ toxicity - single

Hazard statement	Reason for no classification

Specific target organ toxicity - repeated

Hazard statement	Reason for no classification

Environmental hazards

	Hazard statement	Reason for no classification
Hazardous to the aquatic environment		conclusive but not sufficient for classification

Additional hazard classes

Specific concentration limits

Notes

2.2 DSD - DPD

Classification and Labelling according 67/548/EEC (DSD)

EU: REACH

General information

Name bis(2-propylheptyl(phtalate)

(X) Not classified

Status 67/548/EEC self classification

Remarks

Notes

7 Toxicological information

7.1 Toxicokinetics, metabolism and distribution

Endpoint summary: Toxicokinetics, metabolism and distribution

UUID	IUC5-03336232-1f57-4fd1-8b21-24a3659e95c7
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-12-28 17:57:47 CET
Remarks	

Administrative Data

EU: REACH

Discussion

Following oral application of DPHP, 34 % of the oral dose was eliminated via urine as secondary metabolites. Less than 1 % was excreted as the monoester MPHP. Dermal absorption is also very low and was estimated to be less than 0,5 %. Due to its extremely low vapor pressure, only aersols may lead to inhalative uptake which is assumed to be low

Due to its extremely low vapour pressure, DPHP vapour phase concentrations may not attain high

levels, even at the high temperatures used in some industrial conditions (e.g. processing, mixing,

calendering).

At 20°C DPHP has a vapour pressure of 0.000000037 hPa, even at 211 °C the vapor pressure is

only 0.99 hPa. Occupational exposure to vapour will actually be far below these values.

7.1.1 Basic toxicokinetics

Endpoint study record: Analogy 26761-40-0.Basic toxicokinetics

UUID	IUC5-f57708c4-2eef-4436-81db-7041d5714e2a
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-12-28 17:15:13 CET
Remarks	

Administrative Data

other:Risk Assessment, EU: REACH

Purpose flag	supporting study ( ) robust study summary (X) used for classification (X) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliability	2 (reliable with restrictions)
Rationale for reliability	Secondary literature within accepted EU Risk Assessment Report.

Data source

Reference

Reference type	secondary source		
Author	EU	**Year**	2003
Title	EU Risk Assessment Report, DIDP (CAS Nos.: 685151-49-1; 26761-40-0);		
Bibliographic source	Volume 36		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Data access

data published

Materials and methods

Objective of study

toxicokinetics

Test material equivalent to submission substance identity

no

Test material identity

Identifier CAS number

Identity 685151-49-1

Identifier CAS number

Identity 26761-40-0

Test materials

Details on test material

Structurally related C10 Phthalate ester, but not identical to test substance

Administration / exposure

Doses / concentrations

0.1, 11.2 and 1000 mg/kg

Results and discussions

Metabolite characterisation studies

Remarks on results including tables and figures

Via 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, with increasing dose an increasing amount of unabsorbed compound is eliminated (faecal radioactivity associated with parent compound was increased by a factor two between 0.1 and 1,000 mg/kg).

Via dermal route, absorption is very low (most of the unabsorbed dose remained at the skin area at day 7). DIDP showed a very slow excretion, reflecting a slow dermal uptake process: a possible cutaneous tank may be hypothesised, leading to a progressive systemic release, as indicated by the increased amount of radioactivity eliminated in faeces from day 1 to day 7 (Elsisi et al., 1989). The maximum percentage of absorption may be estimated 4% of applied dose in 7 days by analogy with DINP (Midwest Research Institute, 1983).

In humans, skin absorption is still lower than in rat as indicated by in vitro comparative studies, when SSARs (steady state absorption rate) were compared (Mint and Hotchkiss, 1993). Inhaled DIDP aerosol seems readily absorbed. It can be assumed that a part of insoluble particles are cleared from the nasopharyngeal region and swallowed. In the same way, in the tracheobronchial tree the mucociliary transport system leads deposited particles upward to the oropharynx where they are swallowed and pass through the GI tract. Thus, for the risk characterisation, a 100% absorption may be overestimated and a 75% bioavailability seems realistic.

In tissues, DIDP is mainly recovered in GIT, liver, kidneys, by oral or inhalation route, whereas following dermal exposure, muscle and adipose tissue contain most of the dose remaining in the body. Following inhalation, DIDP content in fat tissue is very low, but remains constant from the end of exposure to the end of the observation period (72 hours). No parent DIDP or

monoisodecyl phthalate (MIDP) but only metabolites (the oxidative monoester derivative and phthalic acid) are excreted in urine. In bile, DIDP was not detected in extracts 24 and 72 hours following dosing. The data on end products suggest a cleavage to the monoester and an alcohol moiety, indicating a metabolic scheme comparable to the one reported for DEHP. In feces the monoester oxidative derivative, MIDP as well as DIDP were detected. It is noticeable that metabolic pathway leading to phthalic acid is saturable, and that consequently monoester elimination is increased. DIDP is rapidly eliminated and not accumulated in tissues, less than 1% of the radioactivity was recovered in tissues after 72 hours. By oral and inhalation routes, excretion is shared between urine and faeces. By dermal exposure, only faecal elimination was indicated, but considering the low rate of recovery and by analogy with the two other routes and with the DINP behaviour, the same scheme may be anticipated. In addition, results from the two-generation study suggest a possible transfer of DIDP through the milk when dams are exposed by oral route.

Overall remarks, attachments

Overall remarks

Analogy to DIDP (CAS Nos.: 685151 -49 -1; 26761 -40 -0) within the EU Risk

Endpoint study record: key: Basic toxicokinetics. Wittassek 2007

UUID	IUC5-48f030a6-05e8-423a-b215-87d17781195d
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 11:27:40 CET
Remarks	

Administrative Data

EU: REACH

Purpose flag	key study ( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability	Acceptable publication which meets basic scientific principles

Data source

Reference

Reference type	publication		
Author	Wittassek M and Angerer J	**Year**	2007
Title	Phthalates: metabolism and exposure		
Bibliographic source	Int J Androl. 2008 Apr;31(2):131-8		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Data access

data published

Materials and methods

Type of method

in vivo

Objective of study

excretion

Test guideline

Qualifier	no guideline available
Guideline	

Deviations

Principles of method if other than guideline

Study with human

GLP compliance

no data

Test material equivalent to submission substance identity

yes

Test material identity

Identifier	CAS number
Identity	53306-54-0
Identifier	EC number
Identity	258-469-4
Identifier	IUPAC name
Identity	bis(2-propylheptyl) phthalate

Radiolabelling

no data

Test materials

Details on test material

- Name of test material (as cited in study report): DPHP

Test animals

Species

human

Strain

other: not applicable

Sex

male

Details on test animals and environmental conditions

a healthy male human volunteer, aged 63

Administration / exposure

Route of administration

other: a single oral dose

Vehicle

no data

Duration and frequency of treatment / exposure

single oral dose

Doses / concentrations

data not given

No. of animals per sex per dose

data not given

Control animals

no data

Any other information on materials and methods incl. tables

Results and discussions

Pharmacokinetic studies

Excretion

34% of the applied dose is excreted in urine as hydroxy, oxo and carboxy metabolites. Less than 1 % was excreted in urine as the simple monoester.

Metabolite characterisation studies

Metabolites identified

yes

Details on metabolites

Monopropylheptyl phthalate (MHPH), hydroxy-Monopropylheptylphthalate (OH-MPHP), oxo-Monopropylheptylphthalte (oxo-MPHP) and carboxy-Monopropylhexylphthalate.

Remarks on results including tables and figures

After a single oral application DPHP was hydrolysed to the respective monoester, which underwent further metabolic changes. 34 % of the applied dose was excreted in the urine, most of them as secondary metabolites. As expected, only a minute amount of the applied dose was excreted in the form of the monoester (less than 1 %). According to the authors (personal communication) most of the metabolites were excreted within the first 24 hours after the dosing.

7.1.2 Dermal absorption

Endpoint summary: Dermal absorption

UUID	IUC5-5e50cfd4-f398-4d99-b823-8a3bd9e43153
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-12-28 17:44:21 CET
Remarks	

Administrative Data

EU: REACH

Short description of key information

Based on cross-reading to structurally related C8/C9 or C10 Phthalate esters, dermal absorption is very low

Key parameter (optional)

Absorption rate (%)	.5

Discussion

Skin absorption of chemicals can be described using a simple model which depends only upon

the size of the permeant and its octanol/water partition coefficient (Potts and Guy, 1992, Predicting skin permeability. Pharmaceut. Res. 9(5), 663-669.). The
maximum penetrant flux decreases very rapidly for log P values greater than 2 (Guy and Hadgraft, 1988). The molecular weight is generally considered as presenting less influence (although there was very limited experience with high molecular weight substances), the diffusion coefficient being theoretically inversely proportional to the cube root of molecular weight (ECETOC, 1993). With its very marked lipophilicity and high molecular weight, DPHP
may be inferred to have a very low skin penetration. A comprehensive set of experimental data
about dermal absorption properties of phthalates confirms that skin penetration of the structurally related DIDP (another C10 phthalate) is very low.
Results specific to [14C]-DIDP (NIEHS, 1988; Elsisi et al., 1989, Dermal absorption of phthalate diesters in rats. Fund. Appl. Toxicol. 12,
70-77.) involved dermal absorption of
phthalate diesters (DMP to DIDP) in F 344 rats,*in vivo*. The dose applied to the skin was around
5-8 mg/cm2. The ring-labeled phthalates were applied dissolved in absolute ethanol, with*in situ*
evaporation. The dosed back skin was covered by a circular plastic cap perforated with needle holes. Total excretion was measured at different times.
This study shows that DIDP is markedly less absorbed (ca. 10 times, when comparing faecal +
urinary excretions at day 7) by this route than DEHP.
For DEHP, recovery at 7 days was 86% at the site of application, for a total recovery of 105%.
After 5 days, cumulative excretion data indicate that 5% of the dose was recovered.

For the structurally related DIDP, recovery was 75% at the site of application, for a total recovery of 82% after 7 days.
Cumulative excretion data after 7 days indicate that 0.5% of the dose was recovered in feces. No
radioactivity was recovered in urine. It is noticeable that only faecal elimination was found. The
author implies a preference for biliary excretion when the length of the side chain increases but
this is not consistent with the scheme of elimination observed with DINP and the two other routes where radioactivity was shared between urine and feces. High differences in total recovery hinder a quantitative comparison of data. Muscle, adipose tissue and skin contained
most of the dose remaining in the body. The total absorbed dose after 7 days can be estimated to
be 1%, however this value is possibly underestimated because of the low recovery.
The skin application site was apparently not washed before evaluating DIDP residue. In all cases, dermal uptake decreased when the side chain length increased beyond four carbons. Skin
absorption appeared to decrease with branched alkyl side chains.

In conclusion, a**dermal absorption rate of 0,5 % is used for risk assessment on the dermal route.**

7.2 Acute Toxicity

Endpoint summary: Acute Toxicity

UUID	IUC5-b2eea3d6-b31d-4516-86fc-53a62ee686b4
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 11:31:03 CET
Remarks	

Administrative Data

EU: REACH

Short description of key information

Acute toxicity:
- oral: LD50 >5000 mg/kg bw
- dermal: Ld50 >2000 mg/kg bw
- inhalative: LC50 >20.5 mg/l air (1 h exposure)

Key parameter (optional)

Acute toxicity: oral

Effect level		in	
	LD50	mg/kg bw	5000

Acute toxicity: dermal

Effect level		in	
	LD50	mg/kg bw	2000

Acute toxicity: inhalation

Effect level		in	
	LD50	mg/m³ air	20.5

Discussion

Acute oral toxicity was tested in a study, where five male and five female albino Sherman-Wistar rats were received an oral application of 5000 mg/kg bw of a mixture of 91.3% di-(2-propylheptyl) phthalate and 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl)phthalate (Biosearch Inc., 1982). Prior to dosing, the rats were fasted for 24 hours and body weights were measured. After dosing, food and water were available*ad libitum*and daily observations were recorded for 14 days. Because no deaths and no unusual behavioral signs were observed, the LD50 for acute oral toxicity was estimated as > 5000 mg/kg bw.

To analyze acute dermal toxicity, 2000 mg/kg of a mixture of 91.3% di-(2-propylheptyl) phthalate and 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl)phthalate was applied to the backs of three male

and three female albino rabbits (Biosearch Inc., 1982). The skin sites were previously clipped free of hair and then covered with gauze after application. 24 hours later, the dressings and excess materials were removed and for a period of 14 days, observations and mortalities were noted. Since no mortality and no unusual behavior signs were noted, the LD50 for acute dermal toxicity was determined to be > 2000 mg/kg.
The acute inhalation toxicity of DINP was investigated in a group of 5 male and 5 female albino rats, which were exposed via whole-body inhalation to 20.5 mg/l di-(2-propylheptyl) phthalate aerosol (3-5 microns) of 91.3% purity [8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylexyl) phthalate] for a period of one hour (Biosearch Inc., 1982). Thereby, the exposure was conducted in a 70 L all glass exposure chamber with an air flow rate of 10.0 l/min and a temperature of approximately 21 °C. During the 14 days observation period, no animals died and all gained body weight, although some clinical signs including wet and ruffled fur, agitation, and raspy sounds were noted. However, after 24 hours, the rats appeared normal. Since no mortality occurred and no abnormalities was found after pathological examinations, the LC50 was determined to be >20.5 mg/l after 1 h exposure. Following Haber’s Law, the value for the LC50 after 4 h exposure could be calculated as >5 mg/l air.

Justification for classification or non-classification

Due to the effect levels obtained in the acute toxicity studies, no classification according to EU and GHS criteria is required.

7.2.1 Acute toxicity: oral

Endpoint study record: Key.TSCATS79-1676A.Acute toxicity: oral

UUID	IUC5-48283ee1-1fd3-4a8c-a914-facc73021249
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 11:32:17 CET
Remarks	

Administrative Data

EU: REACH

Purpose flag	key study ( ) robust study summary (X) used for classification (X) used for MSDS

Study result type	experimental result	**Study period**	From 23 May 1979 to 6 Jun 1979
Reliability	2 (reliable with restrictions)		
Rationale for reliability	Comparable to current guideline requirements and scientifically valid with acceptable restrictions.		

Data source

Reference

Reference type	study report		
Author	Biosearch Inc., Nuodex Inc.	**Year**	1982
Title	Mixed C-10 alkyl phthalates (acute oral toxicity - rats)		
Bibliographic source	TSCATS, OTS 206260, Doc I.D. 878210227		
Testing laboratory	Biosearch Inc.	**Report no.**	79-1676A
Owner company	Tenneco Chemicals, inc.		
Company study no.		**Report date**	1982-11-15

Data access

other: Clarification required

Materials and methods

Test type

standard acute method

Limit test

yes

Test guideline

Qualifier	equivalent or similar to

Guideline OECD Guideline 401 (Acute Oral Toxicity)

Deviations yes weight variation is higher than 20% of mean

GLP compliance

no data

Test materials

Test material equivalent to submission substance identity

yes

Details on test material

- Name of test material (as cited in study report): Di-(2-propylheptyl)-phthalate
- Source: Tenneco Chemicals
- Lot/batch No.: R-1034
- Composition of test material, percentage of components: 91.3% Di-(2-propylheptyl)-phthalate; 8.7% mixed 2-propylheptyl/4-methyl-2-propylhexyl-phtalate and 4-di-(4-methyl-2-propy lhexyl) phthalate

Test animals

Species

rat

Strain

other: Sherman Wistar

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS
- Weight at study initiation: 200 - 300 g
- Fasting period before study: 24 h
- Diet (e.g. ad libitum): ad libitum
- Water (e.g. ad libitum): ad libitum

Administration / exposure

Route of administration

oral: gavage

Vehicle

unchanged (no vehicle)

Details on oral exposure

MAXIMUM DOSE VOLUME APPLIED: 5 g/kg bw

Doses

5000 mg/kg bw

No. of animals per sex per dose

5

Control animals

no data

Details on study design

- Duration of observation period following administration: 14 days
- Frequency of observations and weighing: weighing prior to and at the end of study
- Necropsy of survivors performed: yes
- Other examinations performed: clinical signs, body weight

Any other information on materials and methods incl. tables

Results and discussions

Effect levels

Sex	male/female
Endpoint	LD50
Effect level	> 5000 mg/kg bw
95% CL	
Remarks	

Mortality

No mortality

Clinical signs

No unusual behavioral signs were noted.

Body weight

Prior to study: mean 220 g (males), 215 g (females)
End of study: mean 255 g (males), 235 g (females)

Gross pathology

Gross pathological examination revealed nothing remarkable.

Remarks on results including tables and figures

Overall remarks, attachments

Overall remarks

7.2.2 Acute toxicity: inhalation

Endpoint study record: Key.TSCATS79-1676A.Acute toxicity: inhalation

UUID	IUC5-69768536-8f99-43ae-a8ea-cef7e8462574
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 11:39:09 CET
Remarks	

Administrative Data

other:Risk Assessment; Critical study for SIDS endpoint, EU: REACH

Purpose flag	key study ( ) robust study summary (X) used for classification (X) used for MSDS
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability	Comparable to current guideline requirements and scientifically valid with acceptable restrictions.

Data source

Reference

Reference type	study report		
Author	Biosearch Inc., Nuodex Inc.	**Year**	1982
Title	Acute inhalation toxicity - rats		
Bibliographic source	TSCATS, OTS 206260, Doc I.D. 878211987, Nuodex Inc., Biosearch Inc.		
Testing laboratory	Biosearch Inc.	**Report no.**	79-1676A
Owner company	Tenneco Chemicals, Inc.		
Company study no.		**Report date**	1982-11-15

Data access

other: Clarification required

Materials and methods

Test type

standard acute method

Limit test

yes

Test guideline

Qualifier	equivalent or similar to

Guideline OECD Guideline 403 (Acute Inhalation Toxicity)

Deviations yes exposure time was only 1 hour

GLP compliance

no data

Test materials

Test material equivalent to submission substance identity

yes

Details on test material

- Name of test material (as cited in study report): Di-(2-propylheptyl)-phthalate
- Source: Tenneco Chemicals
- Lot/batch No.: R-1034
- Composition of test material, percentage of components: 91.3% Di-(2-propylheptyl)-phthalate; 8.7% mixed 2-propylheptyl/4-methyl-2-propylhexyl-phtalate and 4-di-(4-methyl-2-propylhexyl) phthalate

Test animals

Species

rat

Strain

other: albino rats

Sex

male/female

Administration / exposure

Route of administration

inhalation: aerosol

Type of inhalation exposure

whole body

Vehicle

other: air

Details on inhalation exposure

GENERATION OF TEST ATMOSPHERE / CHAMBER DESCRIPTION
- Exposure apparatus: all glass exposure chamber
- Exposure chamber volume: 70 L
- System of generating particulates/aerosols: The air was passed through a desiccant prior to being passed through the test material.
- Rate of air: 10.0 L/min
- Temperature in air chamber: 70°F

TEST ATMOSPHERE (if not tabulated)
- Particle size distribution: 3 - 5 µm

Analytical verification of test atmosphere concentrations

no concentration was calculated by differential weighing

Duration of exposure

1 h **Remarks**

Concentrations

20.5 mg/l (nominal)

No. of animals per sex per dose

5

Control animals

no

Details on study design

- Duration of observation period following administration: 14 days
- Frequency of observations and weighing: weighing prior to and at the end of study
- Necropsy of survivors performed: yes
- Other examinations performed: clinical signs, body weight

Any other information on materials and methods incl. tables

Results and discussions

Effect levels

Sex	male/female
Endpoint	LC50
Effect level	> 20.5 mg/L air
95% CL	
Exp. duration	1 h
Remarks	aerosol
Sex	male/female
Endpoint	LC50
Effect level	> 5 mg/L air
95% CL	
Exp. duration	4 h
Remarks	calculated according to GHS

Mortality

No mortality

Clinical signs

Immediately after exposure the animals were wet, ruffled, agitated and raspy sounding.
After 24 hours they appeared normal.

Body weight

Prior to study: mean 205 g (males), 200 g (females)
End of study: mean 250 g (males), 235 g (females)

Gross pathology

Gross pathologic examination revealed nothing remarkable.

Remarks on results including tables and figures

According to GHS the value for dust (aerosol) has to be divided by 4 in order to compare 1 hour exposure to a 4 h exposure as recommended in the guideline. Thus, the value would be above 5 mg/l.

Overall remarks, attachments

Overall remarks

7.2.3 Acute toxicity: dermal

Endpoint study record: Key.TSCATS79-1676A.Acute toxicity: dermal

UUID	IUC5-f1e839cd-94b4-4745-a31f-b48bbf0528f1
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 11:41:01 CET
Remarks	

Administrative Data

other:Risk Assessment; Critical study for SIDS endpoint, EU: REACH

Purpose flag	key study ( ) robust study summary (X) used for classification (X) used for MSDS
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability	Comparable to current guideline requirements and scientifically valid

Data source

Reference

Reference type	study report		
Author	Biosearch Inc., Nuodex Inc.	**Year**	1982
Title	Acute dermal toxicity - rabbits		
Bibliographic source	TSCATS, OTS 206260, Doc I.D. 878211988		
Testing laboratory	Biosearch Inc.	**Report no.**	79-1676A
Owner company	Tenneco Chemicals, Inc.		
Company study no.		**Report date**	1982-11-15

Data access

other: Clarification required

Materials and methods

Test type

standard acute method

Limit test

yes

Test guideline

Qualifier	equivalent or similar to

Guideline OECD Guideline 402 (Acute Dermal Toxicity)

Deviations yes weight variation is higher than 20% of mean

GLP compliance

no data

Test materials

Test material equivalent to submission substance identity

yes

Details on test material

- Name of test material (as cited in study report): Di-(2-propylheptyl)-phthalate
- Source: Tenneco Chemicals
- Lot/batch No.: R-1034
- Composition of test material, percentage of components: 91.3% Di-(2-propylheptyl)-phthalate; 8.7% mixed 2-propylheptyl/4-methyl-2-propylhexyl-phtalate and 4-di-(4-methyl-2-propylhexyl) phthalate

Test animals

Species

rabbit

Strain

other: albino

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS
- Weight at study initiation: between 2.0 and 3.0 kg

Administration / exposure

Type of coverage

occlusive

Vehicle

unchanged (no vehicle)

Details on dermal exposure

TEST SITE
- Area of exposure: back of animal
- Preparation: All animals had their backs clipped free 24 h prior to testing. All of the animals had their backs abraded prior to dosing.
- Type of wrap if used: large gauze patches and an impervious wrap around the trunk

REMOVAL OF TEST SUBSTANCE
- Washing (if done): no data
- Time after start of exposure: 24 h

TEST MATERIAL
- Amount(s) applied (volume or weight with unit): 2000 mg/kg bw

- Concentration (if solution): 100%
- Constant volume or concentration used: no, corrected for body weight

Duration of exposure

24 h

Doses

2000 mg/kg bw

No. of animals per sex per dose

3

Control animals

no

Details on study design

- Duration of observation period following administration: 14 days
- Frequency of observations and weighing: prior to and at the end of study
- Necropsy of survivors performed: yes
- Other examinations performed: clinical signs, body weight

Any other information on materials and methods incl. tables

Results and discussions

Effect levels

Sex	male/female
Endpoint	LD50
Effect level	> 2000 mg/kg bw
95% CL	
Remarks	

Mortality

No mortality

Clinical signs

There were no unusual behavioral signs noted.

Body weight

Prior to study: mean 2.44 kg (males), 2.23 kg (females)
End of study: mean 2.75 kg (males), 2.45 kg (females)

Gross pathology

Gross pathologic examination revealed nothing remarkable.

Remarks on results including tables and figures

Overall remarks, attachments

Overall remarks

7.3 Irritation / corrosion

Endpoint summary: Irritation / corrosion

UUID	IUC5-2f26a39e-23e2-4426-ab67-8155638f1d2c
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-06 19:02:13 CET
Remarks	

Administrative Data

EU: REACH

Short description of key information

Irritation:
- skin: not irritant (OECD 404)
- eyes: not irritant (OECD 405)

Key parameter (optional)

Skin irritation / corrosion

not irritating

Eye irritation

not irritating

Discussion

Irritation to skin was evaluated in a study performed under GLP according to guidelines OECD 404, EU Method B.4 and EPA OPPTS 870.2500 (BASF, 2002). Thereby, test patches containing 0.5 mL of di-(2-propylheptyl) phthalate (purity: 99,2 % (sum of isomers)) were applied to the flanks of one male and two female White New Zealand rabbits for 4 hours. The skin sites were evaluated for erythema/eschar and edema formation 1, 24, 48 and 72 hours following removal of the patches. At one hour following patch removal, slight erythema was observed in all animals and persisted in one animal up to 24 hours, but within 48 hours after patch removal, these skin reactions were reversed. The resulting mean irritation scores for 24-72 hours were 0.1 for erythema/eschar and 0.0 for edema, respectively. Thus, di-(2-propylheptyl) phthalate was found to be not irritating to the skin.

In another study, the test sites on the backs of six albino rabbits were clipped free of hair and one side was abraded to allow the substance to penetrate the stratum corneum (Biosearch, Inc., 1982). Then, 0.5 g mixture of 91.3% di-(2-propylheptyl) phthalate and 8.7% 2-propylheptyl/4-methyl-2-propylhexyl and di-(4-methyl-2-propylhexyl)phthalate was applied and covered with gauze, which was removed 24 hours later. The treated areas were examined for erythema, eschar and edema formation using the Draize scale where zero corresponded to no irritation. A second examination was conducted 72 hours following the removal. As result, the scores for

erythema and edema, as well as the primary skin irritation score were found to be 0. Thus, no irritation to skin was found.

Irritation to eyes was tested in a study, which was performed under GLP according to guidelines OECD 405, EU Method B.5 and EPA OPPTS 870.2400 (BASF, 2002). A single ocular application of 0.1 mL of di-(2-propylheptyl) phthalate (purity: 99,2% sum of isomers) was given to one male and two female White New Zealand rabbits and washed out 24 hours later by rinsing with water. The resulting ocular reactions were scored 1, 24, 48 and 72 hours after application. Slight to moderate conjunctival redness and slight discharge were observed up to 24 hours following instillation, but these reactions were reversible in all animals within 48 hours. The average irritation score was 0.0 for corneal opacity, iris effects and chemosis. The conjunctival redness score was 0.3. Thus, di-(2-propylheptyl) phthalate was found to be not irritant to eyes.
In another study, 0.1 g of 91.3% di-(2-propylheptyl) phthalate and 8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4-methyl-2-propylhexyl)phthalate was instilled into the right eyes of six young adult albino rabbits (Biosearch Inc., 1982). While no removal by rinsing was reported, ocular reactions including irritation of the cornea, iris and conjunctivae were examined 1, 24, 48, 72, 120, and 168 hours following the administration. As result, a primary irritation score of 0.0 for all effects was reported. Thus, the tested phthalate mixture was not irritant to eyes.

Justification for classification or non-classification

Due to negative results in guideline study regarding irritation to skin and irritation to eyes, no classification according to EU and GHS criteria is required

7.3.1 Skin irritation / corrosion

Endpoint study record: Key.BASFAG18H0183/022042.Skin irritation / corrosion

UUID	IUC5-c4fc73c3-f8fc-4b69-97b1-bee25527266d
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-06 19:03:33 CET
Remarks	

Administrative Data

other:Risk Assessment; Critical study for SIDS endpoint, EU: REACH

Purpose flag	key study (X) robust study summary (X) used for classification (X) used for MSDS
Study result type	experimental result
Reliability	1 (reliable without restriction)
Rationale for reliability	Guideline study (OECD)

Data source

Reference

Reference type	study report		
Author	BASF AG	**Year**	2002
Title	Acute dermal irritation / corrosion in rabbits		
Bibliographic source	Unpublished report		
Testing laboratory	Experimental Toxicology and Ecology, BASF AG	**Report no.**	18H0183/022042
Owner company	BASF SE		
Company study no.		**Report date**	2002-09-11

Reference type	study report		
Author	BASF AG	**Year**	2002
Title	Acute dermal irritation / corrosion in rabbits		
Bibliographic source	Unpublished report		
Testing laboratory	Experimental Toxicology and Ecology, BASF AG	**Report no.**	18H0183/022042 (amendment No. 1)
Owner company	BASF SE		
Company study no.		**Report date**	2003-04-02

Data access

data submitter is data owner

Materials and methods

Type of method

in vivo

Test guideline

Qualifier	according to
Guideline	OECD Guideline 404 (Acute Dermal Irritation / Corrosion)
Deviations	no
Qualifier	according to
Guideline	EU Method B.4 (Acute Toxicity: Dermal Irritation / Corrosion)
Deviations	no
Qualifier	according to
Guideline	EPA OPPTS 870.2500 (Acute Dermal Irritation)
Deviations	no

GLP compliance

yes (incl. certificate) Experimental Toxicology and Ecology, BASF AG

Test material equivalent to submission substance identity

yes

Test materials

Details on test material

- Name of test material (as cited in study report): Palatinol 10-P
- Test substance No.: 02/0183-1
- Lot/batch No.: 66A/02
- Date of manufacturing: 29.04.2002
- Physical state / appearance: Liquid / colorless
- Analytical purity: 99,2 area -% (sum of isomers)
- Homogeneity: The test substance was homogeneous by visual inspection.
- Stability: stable over the study period acc. to analytical report 031-00063, dated March 31, 2003 of the Central Analytical Department of BASF AG
- Storage conditions: Room temperature

Test animals

Species

rabbit

Strain

New Zealand White

Details on test animals and environmental conditions

TEST ANIMALS
- Strain / quality: New Zealand White Al1077 IN RA (SPF)
- Source: Centre Lago S.A., 01540 Vonnas, France
- Identification: Ear tattoo
- Age at study initiation: about 6 - 7 months

- Weight at study initiation: 3.52 kg - 3.89 kg
- Housing: single housing in stainless steel wire mesh cages with grating, floor area: 3000 cm2
- Diet (e.g. ad libitum): Kliba-Labordiät, Provimni Kliba SA, Kaiseraugst, Switzerland (about 130 g/animal per day); ad libitum
- Water (e.g. ad libitum): tap water; ad libitum
- Acclimation period: at least 5 days before the beginning of the study.

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20 - 24
- Humidity (%): 30 - 70
- Photoperiod (hrs dark / hrs light): 12 / 12

Test system

Type of coverage

semiocclusive

Preparation of test site

other: clipping of fur

Vehicle

unchanged (no vehicle)

Amount/concentration applied

TEST MATERIAL
- Amount(s) applied (volume or weight with unit): 0.5 ml
- Concentration (if solution): 100%

Duration of treatment / exposure

4 hour(s)

Observation period

72 h

Number of animals

3 (2 females, 1 male)

Control animals

other: untreated skin sites of the same animal

Details on study design

TEST SITE
- Area of exposure: Flank of animal
- Site preparation: At least 24 hours before the beginning of the study clipping of the dorsolateral part of the trunk of the animal(s).
- Type of wrap if used: test patch (2.5 cm x 2.5 cm) was moistened with a dose of 0.5 ml of the unchanged liquid test substance.

REMOVAL OF TEST SUBSTANCE
- Washing (if done): yes, with Lutrole and Lutrole : water (1 : 1)
- Time after start of exposure: 4 h

SCORING SYSTEM:
The evaluation of skin reactions is performed according to the guidelines:

Erythema and eschar formation
0 = No erythema
1 = Very slight erythema (barely perceptible)
2 = Well defined erythema
3 = Moderate to severe erythema
4 = Severe erythema (beet redness) to eschar formation preventing grading of erythema

Edema formation
0 = No edema
1 = Very slight edema (barely perceptible)
2 = Slight edema (edges of area well defined by definite raising)
3 = Moderate edema (raised approx. 1 mm)
4 = Severe edema (raised more than 1 mm and extending beyond area of exposure)

Description of any dermal findings not covered by this scale were recorded.

Any other information on materials and methods incl. tables

Results and discussions

Irritation / corrosion results

Irritation parameter	erythema score
Basis	mean
Time point	24-72 h
Score	0.1
Max. score	
Reversibility	fully reversible within: 48 h
Remarks	
Irritation parameter	edema score
Basis	mean
Time point	24-72 h
Score	0
Max. score	
Reversibility	other: no effects
Remarks	

Irritant/corrosive response data

Slight erythema (ER) was observed in all animals during the course of the study. The cutaneous reactions were reversible in all animals within 48 hours after removal of the patch. The average score (24 to 72 hours) for irritation was calculated to be 0.1 for erythema and 0.0 for edema.

Remarks on results including tables and figures

Results:

Readings	Animal	Erythema	Edema	Additional findings
	1	1	0	
1 h	2	1	0	
	3	1	0	
	1	0	0	
24 h	2	0	0	
	3	1	0	
	1	0	0	
48 h	2	0	0	
	3	0	0	
	1	0	0	
72 h	2	0	0	
	3	0	0	
	1	0.0	0.0	
mean 24 - 72 h	2	0.0	0.0	
	3	0.3	0.0	
mean	1	0.1	0.0	

Overall remarks, attachments

Overall remarks

Applicant's summary and conclusion

Interpretation of results

not irritating

Criteria used for interpretation of results

EU

Endpoint study record: TSCATS79-1676A.Skin irritation / corrosion

UUID	IUC5-2c7f57e0-37f1-41ff-9a97-b1b6befb1ecf
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 09:27:01 CET
Remarks	

Administrative Data

Purpose flag	( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability	Comparable to current guideline requirements and scientifically valid

Data source

Reference

Reference type	study report		
Author	Biosearch Inc., Nuodex Inc.	**Year**	1982
Title	Primary skin irritation study - rabbits		
Bibliographic source	TSCATS, OTS 206260, Doc I.D. 878211990		
Testing laboratory	Biosearch Inc.	**Report no.**	79-1676A
Owner company	Tenneco Chemicals, Inc.		
Company study no.		**Report date**	1982-11-15

Data access

other: Clarification required

Materials and methods

Type of method

in vivo

Test guideline

Qualifier	according to
Guideline	other guideline: section 1500.41 - Hazardous Substances and Articles, Administration and Enforcement Regulations, Fed. Reg. Vol. 38, No. 187, p.27019, 27 September 1973
Deviations	

GLP compliance

no data

Test material equivalent to submission substance identity

yes

Test materials

Details on test material

- Name of test material (as cited in study report): Di-(2-propylheptyl)-phthalate
- Source: Tenneco Chemicals
- Lot/batch No.: R-1034
- Composition of test material, percentage of components: 91.3% Di-(2-propylheptyl)-phthalate; 8.7% mixed 2-propylheptyl/4-methyl-2-propylhexyl-phtalate and 4-di-(4-methyl-2-propylhexyl) phthalate

Test animals

Species

rabbit

Strain

other: albino

Test system

Type of coverage

occlusive

Preparation of test site

other: skin of the rabbits was clipped over a wide area, one side of the back was abraded the other side remained intact

Vehicle

unchanged (no vehicle)

Amount/concentration applied

TEST MATERIAL
- Amount(s) applied (volume or weight with unit): 0.5 g
- Concentration (if solution): 100%

Duration of treatment / exposure

24 hour(s)

Observation period

72 h

Number of animals

6

Control animals

no

Details on study design

TEST SITE
- Area of exposure: back of animal
- Type of wrap if used: Gauze patch covered with an impervious warp

REMOVAL OF TEST SUBSTANCE
- Washing (if done): no data
- Time after start of exposure: 24 h

SCORING SYSTEM:
acc. to Draize

Any other information on materials and methods incl. tables

Results and discussions

Irritation / corrosion results

Irritation parameter	erythema score
Basis	mean
Time point	24, 72 h
Score	0
Max. score	4
Reversibility	other: no effects
Remarks	

Irritation parameter	edema score
Basis	mean
Time point	24, 72 h
Score	0
Max. score	4
Reversibility	other: no effects
Remarks	

Irritation parameter	primary dermal irritation index (PDII)
Basis	mean
Time point	24, 72 h
Score	0
Max. score	
Reversibility	other: no effects
Remarks	

Irritant/corrosive response data

Neither on the abraded nor the intact skin any effects according to the scoring for edema, erythema and eschar formations were observed for the observation period (24 h, 72 h).

Remarks on results including tables and figures

Results:

Readings	Animal	Erythema	Edema
24 h	1	0	0
	2	0	0
	3	0	0
	4	0	0
	5	0	0
	6	0	0
72 h	1	0	0
	2	0	0
	3	0	0
	4	0	0
	5	0	0
	6	0	0
mean 24 - 72 h	1	0.0	0.0
	2	0.0	0.0
	3	0.0	0.0
	4	0.0	0.0
	5	0.0	0.0
	6	0.0	0.0
mean		0.0	0.0

Overall remarks, attachments

Overall remarks

Applicant's summary and conclusion

Interpretation of results

not irritating

Criteria used for interpretation of results

EU

7.3.2 Eye irritation

Endpoint study record: Key.BASFAG11H0183/022043.Eye irritation

UUID	IUC5-1ae6bfa2-6fb7-492e-8a7d-6586c4bc2aa5
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-06 19:04:06 CET
Remarks	

Administrative Data

other:Risk Assessment; Critical study for SIDS endpoint, EU: REACH

Purpose flag	key study (X) robust study summary (X) used for classification (X) used for MSDS
Study result type	experimental result
Reliability	1 (reliable without restriction)
Rationale for reliability	Guideline study (OECD)

Data source

Reference

Reference type	study report		
Author	BASF AG	**Year**	2002
Title	Acute eye irritation in rabbits		
Bibliographic source	Unpublished data		
Testing laboratory	Experimental Toxicology and Ecology, BASF AG	**Report no.**	11H0183/022043
Owner company	BASF SE		
Company study no.		**Report date**	2002-09-11

Reference type	study report		
Author	BASF AG	**Year**	2002
Title	Acute eye irritation in rabbits		
Bibliographic source	Unpublished data		
Testing laboratory	Experimental Toxicology and Ecology, BASF AG	**Report no.**	11H0183/022043 (amendment No. 1)
Owner company	BASF SE		
Company study no.		**Report date**	2003-04-02

Data access

data submitter is data owner

Materials and methods

Type of method

in vivo

Test guideline

Qualifier	according to
Guideline	OECD Guideline 405 (Acute Eye Irritation / Corrosion)
Deviations	no
Qualifier	according to
Guideline	EU Method B.5 (Acute Toxicity: Eye Irritation / Corrosion)
Deviations	no
Qualifier	according to
Guideline	EPA OPPTS 870.2400 (Acute Eye Irritation)
Deviations	no

GLP compliance

yes (incl. certificate) Experimental Toxicology and Ecology, BASF AG

Test material equivalent to submission substance identity

yes

Test materials

Details on test material

- Name of test material (as cited in study report): Palatinol 10-P
- Test substance No.: 02/0183-1
- Lot/batch No.: 66A/02
- Date of manufacturing: 29.04.2002
- Physical state / appearance: Liquid / colorless
- Analytical purity: 99,2 area -% (sum of isomers)
- Homogeneity: The test substance was homogeneous by visual inspection.
- Stability: stable over the study period acc. to analytical report 031-00063, dated March 31, 2003 of the Central Analytical Department of BASF AG
- Storage conditions: Room temperature

Test animals

Species

rabbit

Strain

New Zealand White

Details on test animals and environmental conditions

TEST ANIMALS
- Strain / quality: New Zealand White A1077 INRA (SPF)
- Source: Centre Lago S.A., 01540 Vonnas, France
- Identification: Ear tattoo
- Age at study initiation: About 3 - 4 months

- Weight at study initiation: 2.82 kg -2.99 kg
- Housing: Single housing in stainless steel wire mesh cages with grating, floor area: 3000 cm^2
- Diet (e.g. ad libitum): Kliba-Labordiät, Provimi Kliba SA, Kaiseraugst, Switzerland (about 130 g/animal per day); ad libitum
- Water (e.g. ad libitum): Tap water ad libitum; ad libitum
- Acclimation period: At least 5 days before the beginning of the study.

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20 - 24
- Air changes (per hr): 30 - 70
- Photoperiod (hrs dark / hrs light): 12 / 12

Test system

Vehicle

physiol. saline

Amount/concentration applied

TEST MATERIAL
- Amount(s) applied (volume or weight with unit): 0.1 ml
- Concentration (if solution): 100%

Duration of treatment / exposure

24 hour(s)

Observation period

72 h

Number of animals

3 (2 females, 1 male)

Control animals

other: untreated eye of same animal

Details on study design

REMOVAL OF TEST SUBSTANCE
- Washing (if done): yes, tap water
- Time after start of exposure: 24 h

SCORING SYSTEM:
The evaluation of eye irritation is performed according to the guidelines:

Cornea opacity (op): Degree of density (the most dense area is taken for reading)
0 = No ulceration or opacity
1 = Scattered or diffuse areas of opacity (other than slight dulling of normal luster), details of iris clearly visible
2 = Easily discernible translucent area, details of iris slightly obscured
3 = Nacreous area, no details of iris visible, size of pupil barely discernible
4 = Opaque cornea, iris not discernible through the opacity

Area of cornea involved (the assessment of these ocular reactions is performed independent of the quoted guidelines):
1 = >0<=1/4
2 = >1/4<1/2

3 = >1/2<3/4
4 = >3/4

Iris:
0 = Normal
1 = Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperaemia or injection, any of these observations or combination of any thereof, iris still reacting to light (sluggish reaction is positive)
2 = No reaction to light, haemorrhage, gross destruction (any or all of these)

Conjunctivae redness (red): Refers to palpebral and bulbar conjunctivae, cornea and iris
0 = Blood vessels normal
1 = Some blood vessels definitely hyperaemic (injected)
2 = Diffuse, crimson colour, individual vessels not easily discernible
3 = Diffuse beefy red

Chemosis (sw): Lids and/or nictitating membranes
0 = No swelling
1 = Any swelling above normal (includes nictitating membranes)
2 = Obvious swelling with partial eversion of lids
3 = Swelling with lids about half closed
4 = Swelling with lids more than half closed

Discharge (the assessment of these ocular reactions is performed independent of the quoted guidelines):
0 = No discharge
1 = Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)
2 = Discharge with moistening of the lids and hairs just adjacent to lids
3 = Discharge with moistening of the lids and hairs, and considerable area around the eye

Description of any ocular findings not covered by this scale were recorded.

Any other information on materials and methods incl. tables

Results and discussions

Overall irritation / corrosion results

Irritation parameter	cornea score
Basis	mean
Time point	24-72 h
0	
Max. score	4
Reversibility	other: no effects
Remarks	
Irritation parameter	iris score
Basis	mean
Time point	24-72 h
0	
Max.	2

score

Reversibility other: no effects

Remarks

Irritation parameter conjunctivae score

Basis mean

Time point 24-72 h

0.3

Max. score 3

Reversibility fully reversible within: 48 h

Remarks

Irritation parameter chemosis score

Basis mean

Time point 24-72 h

0

Max. score 4

Reversibility other: no effects

Remarks

Irritant/corrosive response data

Slight to moderate conjunctival redness (1 and 24 h) and slight discharge (1 h) were observed initially for 24 h at maximum. The ocular reactions were reversible in all animals within 48 hours after application. The average score (24 to 72 hours) for irritation was calculated to be 0.0 for corneal opacity and for iris, 0.3 for conjunctival redness and 0.0 for chemosis.

Remarks on results including tables and figures

Animal 1: female, 2.82 kg

Animal 2: male, 2.84 kg

Animal 3: female, 2.99 kg

Results.

Readings	Animal	Cornea		Iris	Conjunctival			Symp
		Opacity	Area		Erythema	Chemosis	Discharge	
1h	1	0	0	0	1	0	1	
	2	0	0	0	2	0	1	
	3	0	0	0	1	0	1	
24 h	1	0	0	0	1	0	0	
	2	0	0	0	1	0	0	

	3	0	0	0	1	0	0
48 h	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
72 h	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
mean 24 - 72 h	1	0.0		0.0	0.3	0.0	
	2	0.0		0.0	0.3	0.0	
	3	0.0		0.0	0.3	0.0	
mean	1	0.0		0.0	0.3	0.0	

Overall remarks, attachments

Overall remarks

Applicant's summary and conclusion

Interpretation of results

not irritating

Criteria used for interpretation of results

EU

Endpoint study record: TSCATS79-1676A.Eye irritation

UUID	IUC5-7553f0b2-8efa-4082-bac2-2a9c99eafd9f
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 11:53:17 CET
Remarks	

Administrative Data

Purpose flag	( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability	Comparable to current guideline requirements and scientifically valid

Data source

Reference

Reference type	study report		
Author	Biosearch Inc., Nuodex Inc.	**Year**	1982
Title	Primary eye irritation study - rabbits		
Bibliographic source	TSCATS, 206260, Doc I.D. 878211989		
Testing laboratory	Biosearch Inc.	**Report no.**	79-1676A
Owner company	Tenneco Chemicals, Inc.		
Company study no.		**Report date**	1982-11-15

Data access

other: Clarification required

Materials and methods

Type of method

in vivo

Test guideline

Qualifier	according to
Guideline	other guideline: section 1500.42 - Hazardous Substances and Articles, Administration and Enforcement Regulations, Fed. Reg. Vol. 38, No. 187, p.27019, 27 September 1973.
Deviations	

GLP compliance

no data

Test material equivalent to submission substance identity

yes

Test materials

Details on test material

- Name of test material (as cited in study report): Di-(2-propylheptyl)-phthalate
- Source: Tenneco Chemicals
- Lot/batch No.: R-1034
- Composition of test material, percentage of components: 91.3% Di-(2-propylheptyl)-phthalate; 8.7% mixed 2-propylheptyl/4-methyl-2-propylhexylpthalate and 4-di-(4-methyl-2-propylhexyl) phthalate

Test animals

Species

rabbit

Strain

other: albino

Details on test animals and environmental conditions

TEST ANIMALS
- Age at study initiation: young animals

Test system

Vehicle

unchanged (no vehicle)

Amount/concentration applied

Concentration: 0.1 g
TEST MATERIAL
- Amount(s) applied (volume or weight with unit): 0.1 g
- Concentration (if solution): 100%

Duration of treatment / exposure

The material was not washed out.

Observation period

7 days

Number of animals

6

Control animals

other: untreated eye of same animal

Details on study design

REMOVAL OF TEST SUBSTANCE
- Washing (if done): no

SCORING SYSTEM:
acc. to system in the "Illustrated Guide for Grading Eye Irritation By Hazardoua Substances"

Any other information on materials and methods incl. tables

The eyes were examined at 1, 24, 48, 72 h and 5 and 7 days.

Results and discussions

Overall irritation / corrosion results

Irritation parameter	cornea score
Basis	mean
Time point	24, 48, 72 h
0	
Max. score	4
Reversibility	other: no effects
Remarks	

Irritation parameter	iris score
Basis	mean
Time point	24, 48, 72 h
0	
Max. score	2
Reversibility	other: no effects
Remarks	

Irritation parameter	conjunctivae score
Basis	mean
Time point	24, 48, 72 h
0	
Max. score	3
Reversibility	other: no effects
Remarks	

Irritation parameter	chemosis score
Basis	mean
Time point	24, 48, 72 h
0	
Max. score	4
Reversibility	other: no effects
Remarks	

Irritant/corrosive response data

None of the tissues observed (cornea, iris, and conjunctivae) showed any effects after 1, 24, 48, 72 hrs and 5 and 7 days within this method.

The subject material is not a primary ocular irritant to albino rabbits within the referred methods.

Remarks on results including tables and figures

Results:

Readings	Animal	Cornea		Iris	Conjunctiva		
		Opacity	Area		Redness	Swelling	Dischar
24 h	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	6	0	0	0	0	0	0
48 h	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	6	0	0	0	0	0	0
72 h	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	6	0	0	0	0	0	0
5 d	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	6	0	0	0	0	0	0
7 d	1	0	0	0	0	0	0
	2	0	0	0	0	0	0
	3	0	0	0	0	0	0
	4	0	0	0	0	0	0
	5	0	0	0	0	0	0
	6	0	0	0	0	0	0
mean 24 - 72 h	1	0.0	0.0	0.0	0.0	0.0	0.0
	2	0.0	0.0	0.0	0.0	0.0	0.0
	3	0.0	0.0	0.0	0.0	0.0	0.0
	4	0.0	0.0	0.0	0.0	0.0	0.0
	5	0.0	0.0	0.0	0.0	0.0	0.0
	6	0.0	0.0	0.0	0.0	0.0	0.0
mean		0.0	0.0	0.0	0.0	0.0	0.0

Applicant's summary and conclusion

Interpretation of results

not irritating

Criteria used for interpretation of results

EU

7.4 Sensitisation

Endpoint summary: Sensitisation

UUID	IUC5-4818a043-7f87-413b-b423-e34e08ee7917
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-12-28 18:03:50 CET
Remarks	

Administrative Data

EU: REACH

Skin sensitisation

Short description of key information

Sensitization:
- skin: not sensitizing (modified Buehler test)

Key parameter (optional)

Skin sensitisation

not sensitising

Discussion

The structure of Di-(2-propylheptyl)phthalate did not give any indication for sensitizing properties

(for both the parent and metabolites) by using a quantitative structure-activity relationship (QSAR): the validated OASIS-LMC. This result is supported by an in vivo study wheresensitization to skin was evaluated on five male and five female albino guinea pigs that were treated with 0.5 g of di-(2 -propylheptyl) phthalate of 91.3% purity [8.7% 2-propylheptyl/4-methyl-2-propylhexyl/di-(4 -methyl-2 -propylexyl) phthalate] on the shaved skin of their backs covered by gauze patches (Biosearch Inc. 1982). Following 24 hours contact, the patches were removed and patches with fresh sample were then applied. This procedure was then repeated 10 times. After a following rest period of two weeks, a challenge dose was applied to skin sites different from the original test sites for 24 hours. Resulting irritation effects were evaluated 24 hours after each initial exposure, and 24 and 48 hours after the challenge application using the Draize method. Since no animals showed erythema or edema after 24 and 48 hours, di-(2-propylheptyl) phthalate was found to be not sensitizing to skin.

Respiratory sensitisation

Discussion

Justification for classification or non-classification

QSAR indicated no skin sensitizing potential. Due to the negative result in a

modified Buehler test, no classification according EU and GHS criteria is waranted.

7.4.1 Skin sensitisation

Endpoint study record: TSCATS79-1676A.Skin sensitisation

UUID	IUC5-d640efb3-eb89-47eb-8bd5-9e8016c4d9cd
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-12-28 16:57:13 CET
Remarks	

Administrative Data

other:Risk Assessment; Critical study for SIDS endpoint, EU: REACH

Purpose flag	supporting study ( ) robust study summary (X) used for classification (X) used for MSDS

Study result type	experimental result	**Study period**	From 31 May 1979 To 11 Jul 1979
Reliability	2 (reliable with restrictions)		
Rationale for reliability	Comparable to guideline study with acceptable restrictions		

Data source

Reference

Reference type	study report		
Author	Biosearch Inc., Nuodex Inc.	**Year**	1982
Title	Guinea pig contact dermal irritation/sensitization		
Bibliographic source	TSCATS, OTS 206260, Doc I.D. 878211986		
Testing laboratory	Biosearch Inc.	**Report no.**	79-1676A
Owner company	Tenneco Chemicals, Inc.		
Company study no.		**Report date**	1982-11-15

Data access

data published

Materials and methods

Type of method

in vivo

Type of study

other: Guinea pig contact dermal irritation/sensitization test

Test guideline

Qualifier	equivalent or similar to
Guideline	OECD Guideline 406 (Skin Sensitisation)
Deviations	yes occlusive patch held for 24 hours instead of 6 hours; 10 instead of 20 animals

Principles of method if other than guideline

Modified Buehler-test with 10 inductions

GLP compliance

no data

Test materials

Test material equivalent to submission substance identity

yes

Details on test material

- Name of test material (as cited in study report): Di-(2-propylheptyl)-phthalate
- Source: Tenneco Chemicals
- Lot/batch No.: R-1034
- Composition of test material, percentage of components: 91.3% Di-(2-propylheptyl)-phthalate; 8.7% mixed 2-propylheptyl/4-methyl-2-propylhexylphtalate and 4-di-(4-methyl-2-propylhexyl) phthalate

Test animals

Species

guinea pig

Strain

other: albino

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS
- Weight at study initiation: between 300 and 400 g
- Housing: housed and maintained in compliance with the Animal Welfare Act (Pub. L-94-279) 9 CFR part 3

Test system

Traditional sensitisation test

Route of induction exposure

epicutaneous, occlusive

Route of challenge exposure

epicutaneous, occlusive

Vehicle

unchanged (no vehicle)

Concentration

100%; 0.5 g

No. of animals per dose

5 male and 5 female

Details on study design (Traditional tests)

MAIN STUDY
A. INDUCTION EXPOSURE
- No. of exposures: 10
- Exposure period: 20 d
- Test groups: 10 animals
- Control group: no
- Site: the same intact skin test site
- Patch: gauze patch was placed over the treated area and an impervious material was wrapped tightly around the trunks of the animals to hold the patch in place.
- Frequency of applications: every second day
- Duration: 24 h
- Concentrations: 100%

B. CHALLENGE EXPOSURE
- No. of exposures: 2
- Day(s) of challenge: after a 14 day rest period
- Exposure period: 24 h
- Test groups: 10 animals
- Control group: no
- Site: other skin site than used for induction
- Concentrations: 100%
- Evaluation (hr after challenge): 24, 48 h

SCORING
Sites were examined for irritation (if any) using the Draize Method of Scoring.

Challenge controls

no

Positive control substance(s)

no data

LLNA

Any other information on materials and methods incl. tables

Results and discussion

Traditional sensitisation test

Results of test (except LLNA)

Reading	1st reading
Hours after challenge	24
Group	test group
Dose level	100%
No. with + reactions	0

Total no. in group	10
Clinical observations	
Reading	2nd reading
Hours after challenge	48
Group	test group
Dose level	100%
No. with + reactions	0
Total no. in group	10
Clinical observations	

LLNA

Remarks on results including tables and figures

Individual scoring:

Animal	Sex	Irritation	Readings after application No. 1	2	3	4	5	6	7	8	9	10	Challenge 24 h	48 h
1	M	Erythema	0	0	0	0	0	0	0	0	0	0	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
2	M	Erythema	0	0	0	0	1	1	1	1	1	1	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
3	M	Erythema	0	0	0	0	1	1	1	1	1	1	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
4	M	Erythema	0	0	0	0	0	0	0	0	0	0	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
5	M	Erythema	0	0	0	0	1	1	1	1	1	1	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
6	F	Erythema	0	0	0	0	0	0	0	0	0	0	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
7	F	Erythema	0	0	0	0	0	0	0	0	0	0	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
8	F	Erythema	0	0	0	0	0	1	1	0	1	1	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
9	F	Erythema	0	0	0	0	0	0	0	0	0	0	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0
10	F	Erythema	0	0	0	0	0	0	0	0	0	0	0	0
		Edema	0	0	0	0	0	0	0	0	0	0	0	0

The test substance was not a primary irritant. It is not a skin sensitizer.

Overall remarks, attachments

Overall remarks

Applicant's summary and conclusion

Interpretation of results

not sensitising

Endpoint study record: key: QSAR Skin sensitisation.001

UUID	IUC5-1573a53b-3ba8-402d-baf0-a44a471ea2d2
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-12-28 17:11:53 CET
Remarks	

Administrative Data

EU: REACH

Purpose flag	key study (X) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	(Q)SAR
Reliability	1 (reliable without restriction)
Rationale for reliability	valid QSAR used, DPHP is in the domain of the prediction system

Data source

Reference

Reference type	study report		
Author	BASF SE - Department of Toxicology	**Year**	2009
Title	QSAR on skin sensitizing properties of DPHP and metabolites		
Bibliographic source			
Testing laboratory	BASF SE	**Report no.**	n.a.
Owner company	BASF SE		
Company study no.		**Report date**	

Data access

data submitter is data owner

Materials and methods

Type of method

other: OASIS TIMES MIX V.2.26.2

Type of study

other: QSAR

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier CAS number

Identity 53306-54-0

Identifier EC number

Identity 258-469-4

Identifier IUPAC name

Identity bis(2-propylheptyl) phthalate

Test system

LLNA

Any other information on materials and methods incl. tables

Applicant's summary and conclusion

Interpretation of results

not sensitising

Conclusions

Neither the parent compound (DPHP) nor the 2 putative metabolites (Mono-(2-propylheptyl) phthalate and 2-propylheptanol) showed any indication for skin sensitizing properties

7.5 Repeated dose toxicity

Endpoint summary: Repeated dose toxicity

UUID	IUC5-b2f7d577-32bc-4d9f-9bb9-a9e15279d866
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 14:31:28 CET
Remarks	

Administrative Data

EU: REACH

Short description of key information

Repeated dose toxicity:
- oral: NOAEL = 39 mg/kg bw/d (OECD 408)

Key parameter (optional)

Repeated dose toxicity: oral

Effect level	NOAEL	**in mg/kg bw/day**	39

Target organ

cardiovascular / hematological: other

digestive: liver

Discussion

Repeated dose toxicity of di-(2-propylheptyl) phthalate was evaluated in a study performed under GLP according to guidelines OECD 408 and EU Method B.26 (BASF, 1995).Groups of 10 male and 10 female Wistar rats received di-(2-propylheptyl) phthalate dietary concentrations of 0, 500, 2500, and 15000 ppm in the diet over a period of 3 months. At all doses, no deaths occurred, no clinical findings were found and ophthalmoscopy revealed no treatment-related changes. While there were slightly decreased body weights and retarded body weight gain in male and female rats at 15000 ppm, no effect on food consumption was noted. No effects were found at lower dietary levels. Clinical pathology including hematology and urinalysis showed an increase in alkaline phosphatase, cyanide-insensitive palmitoyl-CoA-oxidation albumin and urinary volume in both sexes of the 15000 ppm dose groups. Also at the high concentration, findings included an increase in platelets in males and creatinine in females, a decrease in hemoglobin, mean corpuscular hemoglobin and chloride in both sexes, decreases in hematocrit and triglycerides in males and decrease in glucose in females. At 2500 ppm only an increase in cyanide-insensitive PCoA-oxidation in females was noted and 500 ppm evoked no treatment-related changes. Although the gross pathology revealed no treatment-related findings at any dose level, the liver weights (absolute and/or relative) were

increased at 2500 and 15000 ppm but not at 500 ppm, which corresponds to the histopathologically observed liver cell hypertrophy at 2500 and 15000 ppm. The increased PCoA, liver weight, and liver hypertrophy are indicative of peroxisomal proliferation in the liver. While at 500 ppm no treatment-related changes were recorded by histopathology, further minor findings in the anterior part of the pituitary gland in male rats and in the thyroid glands in both sexes at 15000 ppm and 2500 ppm. Furthermore, virtually no effects were noted at the organs relevant for reproductive function. Thus, the No Observed Adverse Effect Level (NOAEL) was found to be 500 ppm (39 mg/kg bw/d) in male and female Wistar rats.

In another subchronic study reported in letters submitted to the U.S. EPA, 12 male and 12 female Alpk:APfSD rats per dose were administered di-(2-propylheptyl) phthalate in the diet at concentrations of 0, 40, 420 or 1,000 mg/kg bw/d for a period of 14 weeks (Union Carbide, 1997, 1998).Two additional groups received the diet containing 0 or 12000 ppm and were held for 4 weeks without further treatment. As results, decreases in body weight gain and food consumption were observed at 5000 ppm in males and at 12000 ppm in both sexes. An increased liver weighs with concurrent increases in peroxisome enzyme levels were noted in all treatment groups. The observed hematological changes consisted of decreased hemoglobin levels. Although the sperm velocity was affected at 5000 and 12000 ppm, but no other of the selected sperm parameters as viability, total sperm, static count, percent motile, motile count, total sperm concentration and sperm/g tissue were affected. Moreover, there were no effects at any dose level on the development stages in epididymal sperm. Histology revealed lesions in the zona glomerulosa of the adrenal glands (only minimal at 500 ppm, slight at 5000 ppm and moderate at 12000 ppm) and findings indicative of peroxisome proliferation were noted in the livers at 5000 and 12000 ppm. Thus, the No Observed Adverse Effect Level (NOAEL) was 500 ppm (40 mg/kg/day).

Justification for classification or non-classification

Due to the no adverse effect level obtained in an OECD guideline study, no classification according to EU and GHS criteria is required.

7.5.1 Repeated dose toxicity: oral

Endpoint study record: Key.BASFAG50C0110/94025.Repeated dose toxicity: oral

UUID	IUC5-b98d77e0-f16f-479c-a30c-ba58a16922f1
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 12:30:33 CET
Remarks	

Administrative Data

other:Risk Assessment; Critical study for SIDS endpoint, EU: REACH

Purpose flag	key study (X) robust study summary (X) used for classification (X) used for MSDS		
Study result type	experimental result	**Study period**	From 12 Sep 1994 To 21 Dec 1994
Reliability	1 (reliable without restriction)		
Rationale for reliability	Guideline study (OECD)		

Data source

Reference

Reference type	study report		
Author	BASF AG	**Year**	1995
Title	Subchronic oral toxicity study with Dipropylheptylphthalate in Wistar rats Administration in the diet for 3 months		
Bibliographic source	Unpublished report		
Testing laboratory	Department of Toxicology, BASF AG	**Report no.**	50C0110/94025, Volume I - III
Owner company	BASF SE		
Company study no.		**Report date**	1995-12-21

Data access

data submitter is data owner

Materials and methods

Test type

subchronic

Limit test

no

Test guideline

Qualifier	according to
Guideline	OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)
Deviations	no
Qualifier	according to
Guideline	EU Method B.26 (Sub-Chronic Oral Toxicity Test: Repeated Dose 90-Day Oral Toxicity Study in Rodents)
Deviations	no

GLP compliance

yes Department of Toxicology, BASF AG

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier	CAS number
Identity	53306-54-0

Details on test material

- Name of test material (as cited in study report): Dipropylheptylphthalate
- Test substance No.: 94/110
- Physical state: liquid/colorless
- Analytical purity: 98.7%
- Lot/batch No.: CIW/E - Reg. No. 20 596
- Date of sampling: June 3, 1994
- Storage condition of test material: room temperature, dark and tightly closed

Test animals

Species

rat

Strain

Wistar

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS
- Source: Dr. K. Thomae GmbH, Biberach, Germany
- Identification. ear tattoo
- Age at study initiation: 38 days on arrival
- Weight at study initiation: mean 184 (176 - 194) g for the males, mean 149 (140 - 163) g for the females
- Fasting period before study: about 16 - 20 hours
- Housing: single, DK III stainless steel wire mesh cages (Becker, Castrop-Rauxel, Germany); floor area about 800 cm2
- Diet (e.g. ad libitum): commercial diet (ground Kliba laboratory diet rat/mouse/hamster 343 meal, Klingenthalmuehle AG, Kaiseraugst, Switzerland); ad libitum
- Water (e.g. ad libitum): drinking water ad libitum; ad libitum

- Acclimation period: 7 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20 - 24
- Humidity (%): 30 - 70
- Photoperiod (hrs dark / hrs light): 12 / 12

Administration / exposure

Route of administration

oral: feed

Vehicle

unchanged (no vehicle)

Details on oral exposure

PREPARATION OF DOSING SOLUTIONS:
The test substance was weighed out and thoroughly mixed with a small amount of food in a beaker. Subsequently, a premix was prepared in a BOSCH household mixer by adding an appropriate amount of food and mixing for about 3 minutes. Then corresponding amounts of food, depending on the dose group, were added to this premix in order to obtain the desired concentrations, and mixing was carried out for about 10 minutes in a GEBR. LÖDIGE laboratory mixer.

DIET PREPARATION
- Rate of preparation of diet (frequency): weekly
- Mixing appropriate amounts with (Type of food): 343 meal, supplied by Klingentalmühle AG, Kaiseraugst, Switzerland.
- Storage temperature of food: room temperature

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

The stability of the test substance in the diet at room temperature was proven for 4, 8 and 32 days. The homogeneous distribution of the test substance in the diet was checked in samples of the high and low concentration drawn at the beginning of the study. These analyses served also as concentration controls for low and high concentration. Further concentration control analyses were performed in samples drawn at the start of the administration period (mid concentration) and towards the end of the administration period (all concentrations).

Duration of treatment / exposure

3 months

Frequency of treatment

daily

Doses/concentrations

500, 2500 and 15000 ppm

Basis nominal in diet

39, 196, 1266 mg/kg bw

Basis actual ingested

36, 181 and 1187 mg/kg bw (males)

Basis actual ingested

42, 211, 1344 mg/kg bw (females)

Basis actual ingested

No. of animals per sex per dose

10

Control animals

yes, plain diet

Details on study design

- Dose selection rationale: The doses were chosen an the basis of a previous investigation with 5 animals/sex/group were dosed with concentrations of 0, 1000, 10000 and 20000 ppm (Administration in the diet for two weeks; BASF AG, Project No. 10C0110/94019)

Examinations

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Yes
- Time schedule: A check for overt clinical signs or mortality was made twice a day from Mondays to Fridays and once a day on Saturdays, Sundays and public holidays.
- Cage side observations checked in table were included.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: weekly

BODY WEIGHT: Yes
- Time schedule for examinations: before the start of the administration period in order to randomize the animals. During the conduct of the study, the body weight was determined on day 0 (start of administration period) and thereafter at weekly intervals.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Yes
- Compound intake calculated as time-weighted averages from the consumption and body weight gain data: Yes

FOOD EFFICIENCY:
- Body weight gain in kg/food consumption in kg per unit time X 100 calculated as time-weighted averages from the consumption and body weight gain data: Yes

OPHTHALMOSCOPIC EXAMINATION: Yes
- Time schedule for examinations: Three days prior to the start of the administration period and 91 days after start of the administration period
- Dose groups that were examined: the animals in the highest dose group and in the control group

HAEMATOLOGY: Yes
- Time schedule for collection of blood: 3 days prior and at the end of administration period; in the morning
- Anaesthetic used for blood collection: No

- Animals fasted: No
- How many animals: 10
- Parameters examined: leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, differential blood count, prothrombin time

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: 3 days prior and at the end of administration period; in the morning
- Animals fasted: No
- How many animals: 10/sex/group
- Parameters examined: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum-y-glutamyltransferase, cyanide-insensitive palmitoyl-CoA-oxidation, sodium, potassium, chloride, inorganic phosphate, calcium, urea, creatinine, glucose, total bilirubin, total protein, albumin, globulins, triglycerides, cholesterol, magnesium

URINALYSIS: Yes
- Time schedule for collection of urine: overnight
- Metabolism cages used for collection of urine: Yes
- Animals fasted: No
- Parameters examined: volume, color, turbidity, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, specific gravity, sediment

NEUROBEHAVIOURAL EXAMINATION: No

Sacrifice and pathology

GROSS PATHOLOGY: Yes
HISTOPATHOLOGY: Yes

Statistics

The statistical evaluation and calculation of the data were carried out on the computer systems of the Department of Toxicology of BASF AG:
For the parameters body weight and body weight change a parametric one-way analysis of variance was done via the F-test (ANOVA). If the resulting p-values were equal or less than 0.05, a comparison of each dose group with the control group was carried out. These comparisons were performed simultaneously via DUNNETT's test for the hypothesis of equal means. If the results of this test were significant, labels (* for $p < 0.05$, ** for $p < 0.01$) were printed together with the group means in the tables. Both tests were performed two-sided.
For all clinical chemistry and hematology parameters, excepting the differential blood count, a parametric one-way analysis of variance was done via the F-test (ANOVA). If the resulting p-value was equal or less than 0.05, a comparison of each dose group with the control group was carried out. These comparisons were performed simultaneously via DUNNETT's test for the hypothesis of equal means. If the results of this test were significant, labels (* for $p < 0.05$, ** for $p < 0.01$) were printed together with the group means in the tables. Both tests were performed two-sided.
With the exception of volume, color, turbidity, pH and specific gravity the scale for the urine parameters is divided into 4 sections (0, 1, 2, 3). For the parameter "Nitrite" only a division in two sections (0, 1) is made. The parameters were sorted into 2 classes. This was done for the statistical analysis. A pairwise comparison of each dose group with the control was carried out using FISHER's exact test for the hypothesis of equal proportions. If the results of this test are significant, labels (* for $p < 0.05$, ** for $p < 0.01$) were printed in the tables.

Any other information on materials and methods incl. tables

Results and discussions

Effect levels

Endpoint	NOAEL
Effect level	500 ppm
Sex	male/female
Basis for effect level / Remarks	haematology; clinical chemistry; organ weights; histopathology
Endpoint	NOAEL
Effect level	39 mg/kg bw/day (actual dose received)
Sex	male/female
Basis for effect level / Remarks	haematology; clinical chemistry; organ weights; histopathology

Observations

Details on results

CLINICAL SIGNS AND MORTALITY
- Clinical signs: there were no clinical findings at any dose level
- Mortality: no deaths occurred

BODY WEIGHT AND WEIGHT GAIN
- 15000 ppm: the body weight values of the high dose group were slightly decreased in comparison to the control values. At the end of the administration period values of body weight were 6% below controls in males and 8% below controls in females. Although statistically significant only in females on days 63 to 91, the effects in both sexes were assessed as being substance-related. Corresponding body weight change values at the end of the administration period were 11% below controls in males and 17% below controls in females. Statistical significance was obtained for males on day 7 and for females on several days from day 42 onwards. This was assessed as being substance-related.
- 2500 ppm: no statistically or biologically relevant changes
- 500 ppm: no statistically or biologically relevant changes

FOOD CONSUMPTION AND COMPOUND INTAKE
No statistical changes were observed in all dose groups.

FOOD EFFICIENCY
No statistical changes were observed in all dose groups.

OPHTHALMOSCOPIC EXAMINATION
No substance-related effects were obtained. All findings were spontaneous in nature and within the biological variation of this strain of rats.

HAEMATOLOGY
- 15000 ppm: at the end of the administration period statistically significantly decreased hemoglobin concentrations were found in the peripheral blood of the high dose animals of either sex. Furthermore, in the high dose males statistically significantly decreased

hematocrit values (-5.1%) and increased platelet counts were observed (+20%). In the high dose females mean corpuscular hemoglobin (MCH) was statistically significantly decreased (-5.2%); in the males only a trend towards reduced mean corpuscular hemoglobin was seen.
- 2500 ppm: no statistically or biologically relevant changes
- 500 ppm: no statistically or biologically relevant changes

CLINICAL CHEMISTRY
- 1500 ppm: the blood chemistry examinations revealed statistically significantly decreased chloride concentrations (-2.5% and -3%) and increased albumin levels in the high dose males and females, respectively. However, in the females of the highest dose group only a trend towards increased albumin concentrations was seen. Furthermore, a statistically significant decrease in triglycerides was found in the high dose males (-43%); in the sera of the females statistically significantly increased creatinine concentrations (+9%) and decreased glucose levels (-12.5%) were detected. After 3 month, alkaline phosphatase activities were statistically significantly increased in the sera of the high dose males and females. Moreover, a marked increase in cyanide-insensitive palmitoyl-CoA-oxidation was detected in the liver of the high dose animals of either sex (+824% in male, +680% in females). No other statistically or biologically relevant changes were noted.
- 2500 ppm: statistically significant increases in magnesium (9%) and liver cyanide-insensitive palmitoyl-Coenzyme A-oxidation (47%) in females and a statistically significant increase in albumin (6%) in males. No other statistically or biologically relevant changes were noted.
- 500 ppm: no statistically or biologically relevant changes

URINALYSIS
- 15000 ppm: Males and females of the highest dose group produced slightly greater volumes of urine than the corresponding controls. No other treatment-related changes were seen in the urinalytical parameters examined.
- 2500 ppm: no statistically or biologically relevant changes
- 500 ppm: no statistically or biologically relevant changes

ORGAN WEIGHTS
- 15000 ppm: statistically significant increases in absolute (51.1% M, 59.4% F) and relative (64.2% M, 73.6% F) liver weights; a statistically significant decrease in absolute adrenal weight (15.5%) was observed in males, along with increases in relative kidney (14% M, 10% F) and relative brain (10% M, 8% F) weights
- 2500 ppm: increase in absolute liver weight in females and relative liver weight in males
- 500 ppm: no treatment-related weight changes

GROSS PATHOLOGY
No treatment-related findings at any dose level.

HISTOPATHOLOGY: NON-NEOPLASTIC
- 15000 ppm: liver cell hypertrophy due to peroxisome proliferation in both sexes, increase of basophilic (thyreotrophic cells in the anterior part of the pituitary gland in male rats (8/10), hypertrophy of the follicular epithelium of the thyroid glands in both sexes
- 2500 ppm: liver cell hypertrophy in one male, increase of basophilic (thyreotrophic cells in the anterior part of the pituitary gland in male rats
(3/10), hypertrophy of the follicular epithelium of the thyroid glands in 8 males and 4 females
- 500 ppm: no treatment-related changes

OTHER FINDINGS
There were some additional statistically significant inter-group differences in the results of clinical pathology testing. These deviations are marginal, incidental or inconsistent, when compared with the other sex, or lack dose-response relationship. Accordingly, these findings are considered to be of no toxicological significance.

Remarks on results including tables and figures

Mean body weight (g):

	Day	0 ppm	500 ppm	2500 ppm	15000 ppm
Males	7	183.5	185.2	183.2	185.6
	28	336.6	337	338.7	327.2
	56	412.5	413.7	410.4	388.8
	91	447	458.3	449.7	420.7
Females	0	148.7	149.9	151.9	147.3
	28	212.4	218.6	222.5	209
	56	249.6	254.2	258.2	236.9
	91	269.5	273.5	283.8	248.0*

*p<0.05 (Dunnett's tests and ANOVA)

Mean food consumption (g):

	Day	0 ppm	500 ppm	2500 pppm	15000 ppm
Males	7	26.4	25.7	25.9	21.6
	28	27.4	27.5	27.1	29.2
	56	26.6	26.8	26.1	28
	91	23	23.3	22.5	24.1
Females	0	19.6	19.6	20.5	17.6
	28	19.3	19.9	20.4	20.7
	56	19.6	19.5	19.6	19.9
	91	23	23.3	22.5	24.1

Clinical chemistry, hematology and urinalysis:

			0 ppm	500 ppm	2500 pppm	15000 ppm
Males	HGB	(mM/L)	9.6	9.6	9.8	9.1**
	HCT	(L/L)	0.451	0.452	0.464	0.428*
	MCH	(FM)	1.11	1.09	1.09	1.08
	PLT	(Giga/l)	728	763	770	877**
	ALP	(Mykat/L)	5.42	5.47	5.52	10.28**
	Pal CoA	(Mu/mg P)	6.03	6	9.07	55.75**
	Cl	(mM/L)	104.7	103.9	103.4	102.0*
	Crea	(MyM/L)	55	53.2	55.9	54.5
	Gluc	(mM/L)	7.48	7.79	7.91	7.78
	Alb	(G/L)	33.4	33.38	35.41*	37.52**
	Trig	(G/L)	2.75	3.19	2.25	1.56**
	Urine	ml	4.7	5	4.2	7.2
	HGB	(mM/L)	9.6	9.7	9.5	9.1**
	HCT	(L/L)	0.436	0.44	0.439	0.424
	MCH	(FM)	1.13	1.15	1.14	1.10*

	PLT	(Giga/l)	794	759	692	805
	ALP	(Mykat/L)	4.04	4.32	4.87	5.10*
	Pal CoA	(Mu/mg P)	5.07	5.8	7.46*	39.71**
	Cl	(mM/L)	106.3	106	104.9	102.8**
Females	Crea	(MyM/L)	54.2	56.2	57.9	59.1*
	Gluc	(mM/L)	8.38	7.92	8.29	7.33*
	Alb	(G/L)	36.07	37.28	37.2	38.93
	Trig	(G/L)	1.58	1.9	2.71	1.23
	Urine	ml	3.4	2.6	3.6	4.8

*p<0.05; **p<0.01 (Dunnett's test and ANOVA)

Liver weight:

			0 ppm	500 ppm	2500 pppm	15000 ppm
Males	Absolute	(g)	13.01	14.29	14.76	19.66**
	Relative	(%)	3.08	3.29	3.47	5.05
Females	Absolute	(g)	7.76	7.97	9.28*	12.38**
	Relative	(%)	3.1	3.16	3.47	5.39**

*p<0.05; **p<0.01 (Dunnett's test and ANOVA)

Histopathological incidences:

			0 ppm	500 ppm	2500 pppm	15000 ppm
Males	Liver:	diffuse hypertrophy	0/10	0/10	1/10	10/10
	Pituitary:	increased basophilic cells	0/10	0/10	3/10	8/10
	Thyroid:	hypertrophy	1/10	2/10	8/10	10/10
Females	Liver	diffuse hypertrophy	0/10	0/10	0/10	10/10
	Pituitary:	increased basophilic cells	0/10	0/10	0/10	0/10
	Thyroid:	hypertrophy	0/10	0/10	4/10	10/10

Overall remarks, attachments

Overall remarks

Endpoint study record: TSCATS1997.Repeated dose toxicity: oral

UUID	IUC5-16d7b0d3-cadd-4d03-bdb3-d975366a26b0
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 12:34:11 CET
Remarks	

Administrative Data

Purpose flag	( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability	Acceptable, well documented publication/ study report which meets basic scientific principles

Data source

Reference

Reference type	study report		
Author	Union Carbide Corp.	**Year**	1998
Title	90-day rat feeding study with Bis-2-propylheptyl phthalate		
Bibliographic source	TSCATS, OTS 0001292, Doc. ID. FYI-OTS-0198-1292, Letter		
Testing laboratory		**Report no.**	
Owner company	Union Carbide Corp.		
Company study no.		**Report date**	1998-01-15

Reference type	study report		
Author	Union Carbide Corp.	**Year**	1997
Title	Bis-2-propylheptyl phthalate subchronic feeding study in rats		
Bibliographic source	TSCATS, OTS 0001292, Doc. ID. FYI-OTS-0397-1292, Letter		
Testing laboratory	The Central Toxicology Laboratory (Macclesfield, Cheshire, U.K.).	**Report no.**	
Owner company	Union Carbide Corp.		
Company study no.		**Report date**	1997-03-17

Data access

other: Clarification required

Materials and methods

Test type

subchronic

Limit test

no

Principles of method if other than guideline

90 day feeding study

GLP compliance

no data

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier CAS number

Identity 53306-54-0

Details on test material

- Name of test material (as cited in study report): bis-2-propylheptylphthalate

Test animals

Species

rat

Strain

other: Alpk:APfSD

Sex

male/female

Administration / exposure

Route of administration

oral: feed

Vehicle

no data

Analytical verification of doses or concentrations

no data

Duration of treatment / exposure

14 weeks

Frequency of treatment

daily

Doses/concentrations

500, 5000 and 12000 ppm

Basis nominal in diet

ca. 40, 420 and 1000 mg/kg bw

Basis nominal in diet

No. of animals per sex per dose

12

Control animals

yes, concurrent vehicle

Details on study design

- Post-exposure period: 4 weeks (only 0 and 1000 mg/kg bw (12000ppm))

Examinations

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: No data

DETAILED CLINICAL OBSERVATIONS: No data

BODY WEIGHT: Yes
- Time schedule for examinations: no data

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: No data
- Compound intake calculated as time-weighted averages from the consumption and body weight gain data: No data

FOOD EFFICIENCY:
- Body weight gain in kg/food consumption in kg per unit time X 100 calculated as time-weighted averages from the consumption and body weight gain data: No data

OPHTHALMOSCOPIC EXAMINATION: No data

HAEMATOLOGY: Yes
- Time schedule for collection of blood: No data
- Anaesthetic used for blood collection: No data
- Animals fasted: No data
- How many animals: No data

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: No data
- Animals fasted: No data
- How many animals: No data

URINALYSIS: No data

NEUROBEHAVIOURAL EXAMINATION: No data

Sacrifice and pathology

GROSS PATHOLOGY: Yes
HISTOPATHOLOGY: Yes

Any other information on materials and methods incl. tables

Results and discussions

Effect levels

Endpoint	NOAEL
Effect level	500 ppm
Sex	male/female
Basis for effect level / Remarks	body weight; haematology; clinical chemistry; organ weights; histopathology
Endpoint	NOAEL
Effect level	40 mg/kg bw/day (nominal)
Sex	male/female
Basis for effect level / Remarks	body weight; haematology; clinical chemistry; organ weights; histopathology

Observations

Details on results

BODY WEIGHT AND WEIGHT GAIN
- 12000 ppm: Significant decreases in body weight gain were noted at 12000 ppm in both sexes (23% in males, 19% in females). This difference in weight gain was partially resolved by the end of the 4 week recovery period
- 5000 ppm: slightly reduced in males (6%)
- 500 ppm: no changes

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study)
- 12000 ppm: decrease in food consumption
- 5000 ppm: no changes
- 500 ppm: no changes

HAEMATOLOGY
- 12000 ppm: in both sexes reduction in red blood cell count, hemoglobin and hematocrit with in some instances associated changes in red blood cellular indices and an increase in platelet count
- 5000 ppm: in males reduction in red blood cell count, hemoglobin and hematocrit with in some instances associated changes in red blood cellular indices and an increase in platelet count
- 500 ppm: no changes

CLINICAL CHEMISTRY

- 12000 ppm: decreased plasma sodium concentrations and increased plasma potassium concentrations in both sexes; increased cyanide insensitive palmitoyl CoA activity, decreases in plasma cholesterol and triglycerides.
- 5000 ppm: increased cyanide insensitive palmitoyl CoA activity, decreases in plasma cholesterol arnyl triglycerides.
- 500 ppm: no changes

ORGAN WEIGHTS
Increased liver weights with concurrent increases in peroxisome enzyme levels were noted in all treatment groups

HISTOPATHOLOGY: NON-NEOPLASTIC
- Testes: effects were related solely to velocity measurements. At the end of die 4 week recovery period similar effects were not observed in any of the velocity indices. Other indices of sperm viability were unaffected by treatment including, total sperm, static count, percent motile, motile count, total sperm concentration and sperm/g tissue. There were no effects at any of the dose levels on the stages development in epididymal sperm.
- Adrenal gland: characteristic lesion in the adrenals described as vacuolation of the zona glomerulosa in both sexes at all doses; the severity of the lesion was a clearly dose related predominantly described as minimal in the 500 ppm, slight in the 5000 ppm and moderate in the 12000 ppm dose group
- Liver: lesions in the livers of both sexes in the 12000 and 5000 ppm concentration groups consistent with peroxisome proliferation

Remarks on results including tables and figures

Sperm parameters:

	Main study				Recovery	
	0 ppm	500 ppm	5000 ppm	12000 ppm	0 ppm	12000 ppm
Velocity (straight-line velocity)	61.1 ± 8.3	57.6 ± 8.9	54.4 ± 10.9	46.0 ± 11.1**	44.1 ± 17.8	37.9 ± 18.5
Velocity (curvilinear velocity)	231 ± 17.7	234 ± 17.1	215 ± 25.7	202.3 ± 26.6*	197.6 ± 39.1	187.3 ± 38.7
Velocity (average path velocity)	101.9 ± 9.9	97.5 ± 6.9	91.8 ± 8.9*	85.7 ± 10.8**	83.7 ± 16.4	78.8 ± 17.3
Sperm motility (%)	84 ± 3.2	81 ± 5.5	81 ± 3.8	80 ± 7.9	68 ± 19	71 ± 1
Total sperm	439.0 ± 163.9	335.8 ± 97.7	376.5 ± 106.0	461.2 ± 150.9	-	-
Static count	67.0 ± 18.5	62.5 ± 16.3	72.0 ± 23.7	93.7 ± 64.4	-	-
Motile count	372.0 ± 148.3	273.3 ± 91.8	304.5 ± 88.9	367.5 ± 116.3	-	-
Total concentration	35.5 ± 14.0	28.2 ± 8.0	32.5 ± 9.0	40.1 ± 12.8	-	-
Sperm/g tissue	161.0 ± 69.7	132.2 ± 37.2	156.7 ± 43.9	197.4 ± 71.6	-	-

* p<0.05; **p<0.01

Overall remarks, attachments

Overall remarks

The NOAEL of 500 ppm was due to a dose related severity of lesion in the zona glomerulosa in the adrenals, described as minimal in the 500 ppm concentration groups (female and male). This effect was discussed to be not adverse because it is seen to be associated with the synthesis of steroid hormones, including aldosterone. Steroid hormones are metabolized by mixed function oxidases enzymes implicated in proliferation of peroxisomes. Also, histopathological lesions in the livers in the dose groups 5000 and 12000 ppm of both sexes were argued to be consistent with peroxisome proliferation and not adverse.

The meaning of the significantly reduced sperm velocity at the concentration of 12000 ppm was described to be unknown. No other indices of sperm viability were affected. After the recovery period no differences between the highest dose and control males were found. A hint for explanation may be the nutritional status. The highly reduced body weights in the highest dose groups have to be seen as adverse.

7.6 Genetic toxicity

Endpoint summary: Genetic toxicity

UUID	IUC5-b0ea5716-009d-436b-b306-3f8d2bcf7fc6
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 14:35:14 CET
Remarks	

Administrative Data

EU: REACH

Short description of key information

Genetic toxicity:
- in vitro: negative (OECD 471); negative (Analogies CAS 26761-40-0, CAS 119-06-2)
- in vivo: negative (Analogy CAS 26761-40-0)

Key parameter (optional)

Genetic toxicity

negative

Discussion

Genetic toxicity*in vitro*was evaluated in an Ames test performed under GLP according to guidelines OECD 471 and EU Method B.13/14 (BASF, 1995). In this study,*Salmonella typhimurium*strains TA98, TA100, TA1535 and TA1537 were treated with di-(2-propylheptyl) phthalate at concentrations of 20 to 5000 µg/plate using a standard plate test and pre-incubation procedure with and without metabolic activation. Thereby, three plates per test were prepared in duplicate using test substance and positive controls. Since no mutagenic at all doses was observed in all strains used, di-(2-propylheptyl) phthalate was found to be not mutagenic bacteria in vitro.

Due to the lack of data regarding genetic toxicity in mammalian cells*in vitro*, studies with a mix of the structural homologues containing six phthalate esters consisting of C7, C9, and C11 ester side chains (DIDP) could be taken into account for assessment. In this study, mouse lymphoma L5178Y cells were treated with DIDP in acetone at concentration of 2000 nl/ml to 10000 nl/ml without and metabolic activation and at concentrations of 250 nl/ml to 2000 nl/ml with metabolic activation for 4 hours (EU Risk Assessment DIDP, 2003). As result, no increase in mutant frequency was observed in the presence or absence of metabolic activation. Under conditions of the study DIDP was non-mutagenic in the mouse lymphoma assay with or without metabolic activation, which also could be expected for di-(2-propylheptyl) phthalate due to structural similarities.
In another study, the structural analogue ditridecyl phthalate (CAS 119-06-2) was tested in an chromosomal aberration test performed according to

guidelines OECD 473 and Guidelines for Screening Mutagenicity Testing of Chemicals (). Chinese hamster lung (CHL) cells were treated with concentrations of 0, 1188, 2375 and 4750 µg/ml using DMSO as a solvent with and without metabolic activation (Japan Ministry of Health and Welfare). As result, no toxicity and no structural chromosomal aberrations or polyploidy was detected up to the highest concentration in CHL cells, which also could be expected for di-(2-propylheptyl) phthalate due to structural similarities.
The structural analogue ditridecyl phthalate (CAS 119-06-2) was found to be non-mutagenic in the*Escherichia coli*reverse mutation assay, when tested at concentrations of 156, 313, 625, 1250, 2500, and 5000 µg/plate in DMSO with and without metabolic activation (Japan Ministry of Health and Welfare). Thereby, the testing was conducted according to the Guidelines for Screening Mutagenicity Testing of Chemicals () and OECD Guideline No. 472. Under the conditions of this test, di-C13 phthalate ester did not induce gene mutations in*E. coli*WP2 uvrA. No toxicity was observed up to a concentration of 5000 µg/plate, with or without metabolic activation. Due to structural similarities, the same result could be also expected for di-(2-propylheptyl) phthalate
A published study reported the testing of Di-C7-11 PE (a mixture of six phthalate esters consisting of C7, C9, and C11 ester side chains) and Di-13 PE in a mouse lymphoma assay (Barber et al., 2000). The mouse lymphoma L5178Y cells were treated with Di-C7-11 PE at concentrations of 0.125 to 6 µl/ml and Di -13 PE at concentrations of 1 to 10 µl/ml, respectively (Barber*et al*., 2000). The used mouse lymphoma cells were seeded into a series of tubes at 6 x 10^6cells per tube and the mutant frequencies were calculated after 10-14 days of incubation (at each dose level, triplicate plates). While at the highest doses some cytotoxicity was noted, no increase in the incidence of mutations was found. Thus, the test substances were non-mutagenic in the mouse lymphoma assay with or without metabolic activation, which also could be expected for di-(2-propylheptyl) phthalate due to structural similarities.

For the evaluation of the genetic toxicity in vivo, studies with structural analogues could be taken into account since no data with di-(2-propylheptyl) phthalate could be found.
In a micronucleus test with a mix of the structural homologues containing six phthalate esters consisting of C7, C9, and C11 ester side chains (DIDP), male and female CD-1 mice received doses of 1, 250, 2500 and 5000 mg/kg and bone marrow was prepared 24, 48 and 72 hours later (OECD SIDS; 2003). Since no effects on micronucleated polychromatophile erythrocytes were detected, DIDP was found to be not clastogenic in the mouse bone marrow micronucleus assay, which also could be expected for di-(2-propylheptyl) phthalate due to structural similarities.
The same negative result was found in another micronucleus test with the structural analogues Di-C7-11 PE (a mixture of six phthalate esters consisting of C7, C9, and C11 ester side chains) up to 2000 mg/kg bw and Di-C13 PE at concentrations up to 5000 mg/kg bw (McKee et al., 2000).

Justification for classification or non-classification

Due to the negative results obtained in studies*in vitro*together with the negative results in*in vivo*with the structural analogue DIDP, no classification according to EU and GHS criteria is required.

7.6.1 Genetic toxicity in vitro

Endpoint study record: Key.BASFAG40M0110/944241.genetic toxicity in vitro.Ames

UUID	IUC5-b027fa82-97f8-4bc5-a420-73e9c5c084a9
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-03 19:30:48 CET
Remarks	

Administrative Data

other:Risk Assessment; Critical study for SIDS endpoint, EU: REACH

Purpose flag	key study (X) robust study summary (X) used for classification (X) used for MSDS
Study result type	experimental result
Reliability	1 (reliable without restriction)
Rationale for reliability	Guideline study (OECD)

Data source

Reference

Reference type	study report		
Author	BASF AG	**Year**	1995
Title	REPORT on the Study of Dipropylheptylphthalate in the AMES TEST		
Bibliographic source	Unpublished report		
Testing laboratory	Department of Toxicology, BASF AG	**Report no.**	40M0110/944241
Owner company	BASF SE		
Company study no.		**Report date**	1995-07-03

Data access

data submitter is data owner

Materials and methods

Type of genotoxicity

gene mutation

Type of study

bacterial reverse mutation assay (e.g. Ames test)

Test guideline

Qualifier	according to
Guideline	OECD Guideline 471 (Bacterial Reverse Mutation Assay)
Deviations	

Qualifier	according to
Guideline	EU Method B.13/14 (Mutagenicity - Reverse Mutation Test Using Bacteria)
Deviations	

GLP compliance

yes Department of Toxicology, BASF AG

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier	CAS number
Identity	53306-54-0

Details on test material

- Name of test material (as cited in study report): Dipropylheptylphthalate
- Test substance No.: 94/110
- Date of filling: June 3, 1994
- Physical state: Colorless liquid
- Lot/batch No.: CIW/F-Reg. Nr. 20596
- Storage condition of test material: Room temperature (protected from light)

Method

Target gene

his

Species/strain

Species/strain	S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
Details on mammalian cell lines (if applicable)	
Additional strain characteristics	not applicable
Metabolic activation	with and without
Metabolic activation system	Aroclor 1254-induced rat liver S9-mix

Test concentrations

20, 100, 500, 2500 and 5000 µg/plate

Vehicle

- Vehicle(s)/solvent(s) used: Acetone

Controls

Negative controls	yes
Solvent / vehicle controls	yes
True negative controls	no data
Positive controls	yes
Positive control substance	other: 2-aminoanthracene; 2.5 µg dissolved in DMSO for TA 100, TA 98, TA 1537 and TA 1535
Remarks	with metabolic activation
Negative controls	yes
Solvent / vehicle controls	yes
True negative controls	no
Positive controls	yes
Positive control substance	other: N-methyl-N'-nitro-N-nitrosoguanidine (MNNG); 5 µg dissolved in DMSO for TA 100 and TA 1535
Remarks	without metabolic activation
Negative controls	yes
Solvent / vehicle controls	yes
True negative controls	no
Positive controls	yes
Positive control substance	other: 4-nitro-o-phenylendiamine; 10 µg dissolved in DMSO for TA 98
Remarks	without metabolic activation
Negative controls	yes
Solvent / vehicle controls	yes
True negative controls	no
Positive controls	yes
Positive control substance	9-aminoacridine 100 µg dissolved in DMSO for TA 1537
Remarks	without metabolic activation

Details on test system and conditions

METHOD OF APPLICATION: in agar (plate incorporation) and preincubation

DURATION
- Preincubation period: 20 min, 37°C
- Exposure duration: 48 h, 37°C

NUMBER OF REPLICATIONS: 3

DETERMINATION OF CYTOTOXICITY
- Method: relative total growth

Evaluation criteria

In general, a substance to be characterized as positive in the Ames test has to fulfill the following requirements:
- doubling of the spontaneous mutation rate (control)
- dose-response relationship
- reproducibility of the results

Any other information on materials and methods incl. tables

Results and discussions

Test results

Species/strain	S. typhimurium TA 1535, TA 1537, TA 98 and TA 100
Metabolic activation	with and without
Test system	all strains/cell types tested
Genotoxicity	negative
Cytotoxicity	no
Vehicle controls valid	yes
Negative controls valid	not applicable
Positive controls valid	yes

Additional information on results

TEST-SPECIFIC CONFOUNDING FACTORS
- Precipitation: A precipitation was found from about 500 µg/plate onward

Remarks on results including tables and figures

Results standard plate assay:

Dose µg/plate	metabolic activation	TA98 Trial 1	TA98 Trial 2	TA98 Trial 3	TA100 Trial 1	TA100 Trial 2
0	+	50	38	38	128	118

20	+	46	35	30	106	117
100	+	34	27	49	130	127
500	+	40	31	30	108	111
2500	+	34	35	51	147	125
5000	+	32	33	40	144	124
2.5 µg 2-Aminoanthracene	+	628	591	599	1080	997
0	-	33	31	31	118	144
20	-	18	35	33	132	153
100	-	31	27	33	128	127
500	-	34	25	36	120	120
2500	-	40	36	28	142	138
5000	-	33	29	27	157	155
5 µg MNNG	-				1560	1700
10 µg 4-Nitro-o-phenylendiamin	-	640	533	386		
100 µg 9-amninoacridine	-					

Preincubation test:

Dose µg/plate	metabolic activation	TA98 Trial 1	TA98 Trial 2	TA98 Trial 3	TA100 Trial 1	TA100 Trial 2
0	+	48	46	31	112	98
20	+	49	48	43	88	118
100	+	32	47	45	73	91
500	+	42	48	47	110	86
2500	+	47	59	49	104	91
5000	+	53	48	56	94	93
2.5 µg 2-Aminoanthracene	+	599	649	624	585	529
0	-	49	55	47	136	95
20	-	50	60	35	105	134
100	-	35	56	43	103	100
500	-	38	47	41	107	112
2500	-	43	32	47	89	94
5000	-	50	49	38	122	121
5 µg MNNG	-				555	690
10 µg 4-Nitro-o-phenylendiamin	-	1340	1460	1450		
100 µg 9-amninoacridine	-					

Overall remarks, attachments

Overall remarks

Dipropylheptylphthalate was not mutagenic in the Ames test under the chosen experimental conditions.

Applicant's summary and conclusion

Interpretation of results

negative

Endpoint study record: Analogy 26761-40-0.Genetic toxicity in vitro.MLA

UUID	IUC5-b799ed7d-bb9e-4cbd-aa17-38f3687dfda0
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 13:25:37 CET
Remarks	

Administrative Data

other:Risk Assessment

Purpose flag	key study ( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliability	2 (reliable with restrictions)
Rationale for reliability	Secondary literature within EU Risk Assessment Report.

Data source

Reference

Reference type	secondary source		
Author	EU	**Year**	2003
Title	EU Risk Assessment Report, DIDP (CAS Nos.: 685151-49-1; 26761-40-0)		
Bibliographic source	Volume 36		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	
Reference type	study report		
Author	Hazleton Biotechnologies Company	**Year**	1986
Title	Mutagenicity of 1 L in a Mouse Lymphoma Mutation Assay		
Bibliographic source	Project N° 20989 submitted to CMA		
Testing laboratory	Hazleton Biotechnologies Company	**Report no.**	
Owner company	Hazleton Biotechnologies Company		
Company study no.	20989	**Report date**	

Data access

data published

Materials and methods

Type of genotoxicity

gene mutation

Type of study

mammalian cell gene mutation assay

Test guideline

Qualifier	according to
Guideline	other guideline: 431 FDA modified.
Deviations	no data

GLP compliance

yes Hazleton Biotechnologies Company

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	26761-40-0
Identifier	CAS number
Identity	68515-49-1

Details on test material

DIDP (CAS 26761-40-0 & 68515-49-1)

Method

Target gene

TK

Species/strain

Species/strain	mouse lymphoma L5178Y cells
Details on mammalian cell lines (if applicable)	- Type and identity of media: RPMI 1640 medium - Properly maintained: yes - Periodically checked for Mycoplasma contamination: yes
Additional strain characteristics	
Metabolic activation	with and without
Metabolic activation system	S9 fraction of rat liver

Test concentrations

without metabolic activation: 2000, 4000, 5000, 6000, 8000, 10000 nl/ml
with metabolic activation: 250, 500, 1000, 2000 nl/ml

Vehicle

- Vehicle(s)/solvent(s) used: acetone
- Justification for choice of solvent/vehicle: due to limited solubility in medium

Controls

Negative controls	yes
Solvent / vehicle controls	yes acetone
True negative controls	no
Positive controls	yes
Positive control substance	ethylmethanesulphonate 0.25 - 0.5 µl/ml
Remarks	without metabolic activation
Negative controls	yes
Solvent / vehicle controls	yes acetone
True negative controls	no
Positive controls	yes
Positive control substance	3-methylcholanthrene 1.0 - 4.0 µg/ml
Remarks	with metabolic activation

Details on test system and conditions

Exposure time: 4 hours
The test material was incompletely soluble and formed oily droplets at all concentrations.

METHOD OF APPLICATION: in medium

DURATION
- Exposure duration: 4 h
- Expression time (cells in growth medium): 48 h
- Selection time (if incubation with a selection agent): 10 - 14 days

DETERMINATION OF CYTOTOXICITY
- Method: cloning efficiency

Results and discussions

Test results

Species/strain	mouse lymphoma L5178Y cells
Metabolic	with and without

activation	
Test system	all strains/cell types tested
Genotoxicity	negative
Cytotoxicity	yes
Vehicle controls valid	yes
Negative controls valid	yes
Positive controls valid	yes

Additional information on results

TEST-SPECIFIC CONFOUNDING FACTORS
- Water solubility: incomplete solubility

Remarks on results including tables and figures

The test DIDP was considered non mutagenic under nonactivation and activation conditions.

No increase in mutant frequency was observed in the presence or absence of metabolic activation.

Overall remarks, attachments

Overall remarks

Analogy to DIDP (CAS 26761 -40 -0 & 68515 -49 -1) within a EU Risk Assessment for DIDP.

Applicant's summary and conclusion

Interpretation of results

negative

Endpoint study record: Analogy 119 -06 -2.Genetic toxicity in vitro.cyto

UUID	IUC5-ca0e3d50-abb1-4df2-b76c-f5e7a6b65c32
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 11:14:18 CET
Remarks	

Administrative Data

other:Risk Assessment

Purpose flag	( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliability	2 (reliable with restrictions)
Rationale for reliability	Secondary literature within accepted OECD-SIDS.

Data source

Reference

Reference type	secondary source		
Author	OECD	**Year**	2004
Title	OECD SIDS, High Molecular Weight Phthalate Esters (HMWPE)		
Bibliographic source	SIAM 19, Berlin		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Data access

data published

Materials and methods

Type of genotoxicity

chromosome aberration

Type of study

in vitro mammalian chromosome aberration test

Test guideline

Qualifier	according to
Guideline	OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test)

Deviations

Principles of method if other than guideline

Testing was conducted under the Guidelines for Screening Mutagenicity Testing of Chemicals (Japan).

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	119-06-2

Details on test material

Di-C13 PE

Confidential details on test material

Method

Species/strain

Species/strain	other: Chinese hamster lung (CHL) cells
Details on mammalian cell lines (if applicable)	
Additional strain characteristics	
Metabolic activation	with and without
Metabolic activation system	

Test concentrations

0, 1188, 2375 and 4750 µg/ml

Controls

Negative controls	
Solvent / vehicle controls	yes DMSO
True negative controls	
Positive controls	yes

Positive control substance

Remarks

Results and discussions

Test results

Species/strain	other: Chinese hamster lung (CHL) cells
Metabolic activation	with and without
Test system	all strains/cell types tested
Genotoxicity	negative
Cytotoxicity	
Vehicle controls valid	
Negative controls valid	
Positive controls valid	

Remarks on results including tables and figures

Under the conditions of this test, di-C13 PE did not induce structural chromosomal aberrations or polyploidy in CHL cells with or without an exogenous metabolic system. No toxicity was observed up to a concentration of 4750 µg/plate.

Overall remarks, attachments

Overall remarks

Analogy to Di-C13 PE (CAS No. 119 -06 -2)

Endpoint study record: Analogy 119 -06 -2.Genetic toxicity in vitro.Ames

UUID	IUC5-bcb326cb-4dc1-4c6e-a16b-46c083ae67f6
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 11:14:13 CET
Remarks	

Administrative Data

other:Risk Assessment, EU: BPD

Purpose flag	( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliability	2 (reliable with restrictions)
Rationale for reliability	Secondary literature within accepted OECD-SIDS.

Data source

Reference

Reference type	secondary source		
Author	OECD	**Year**	2004
Title	OECD SIDS, High Molecular Weight Phthalate Esters (HMWPE)		
Bibliographic source	SIAM 19, Berlin		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Data access

data published

Materials and methods

Type of genotoxicity

gene mutation

Type of study

bacterial reverse mutation assay (e.g. Ames test)

Test guideline

Qualifier	according to
Guideline	OECD Guideline 472 (Genetic Toxicology: Escherichia coli, Reverse Mutation

Assay)

Deviations

Principles of method if other than guideline

Testing was conducted under the Guidelines for Screening Mutagenicity Testing of Chemicals (Japan).

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	119-06-2

Details on test material

Di-C13 PE

Method

Species/strain

Species/strain	E. coli WP2 uvr A
Details on mammalian cell lines (if applicable)	
Additional strain characteristics	
Metabolic activation	with and without
Metabolic activation system	

Test concentrations

156, 313, 625, 1250, 2500 and 5000 µg/plate (in DMSO)

Results and discussions

Test results

Species/strain	E. coli WP2 uvr A
Metabolic activation	with and without
Test system	all strains/cell types tested
Genotoxicity	negative
Cytotoxicity	
Vehicle controls valid	
Negative	

controls valid

Positive controls valid

Remarks on results including tables and figures

Under the conditions of this test, di-C13 phthalate ester did not induce gene mutations in E. coli WP2 uvrA. No toxicity was observed up to a concentration of 5000 µg/plate, with or without metabolic activation.

Overall remarks, attachments

Overall remarks

Analogy to Di-C13 PE (CAS No. 119 -06 -2)

Endpoint study record: Analogy mix.Genetic toxicity in vitro.MLA

UUID	IUC5-9dbbad5b-e310-4c7c-bf43-af117d494442
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-03 19:34:06 CET
Remarks	

Administrative Data

other:Risk Assessment

Purpose flag	( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliability	2 (reliable with restrictions)
Rationale for reliability	Secondary literature within accepted OECD-SIDS.

Data source

Reference

Reference type	secondary source		
Author	OECD	**Year**	2004
Title	OECD SIDS, High Molecular Weight Phthalate Esters (HMWPE)		
Bibliographic source	SIAM 19, Berlin		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Data access

data published

Materials and methods

Type of genotoxicity

gene mutation

Type of study

mammalian cell gene mutation assay

Principles of method if other than guideline

(Barber et al., 2000)

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	119-06-2

Details on test material

-Di-C7-11 PE (a mixture of six phthalate esters consisting of C7, C9, and C11 ester side chains)
-Di-C13 PE (CAS 119-06-2)

Method

Species/strain

Species/strain	mouse lymphoma L5178Y cells
Details on mammalian cell lines (if applicable)	
Additional strain characteristics	
Metabolic activation	with and without
Metabolic activation system	

Test concentrations

0.125 to 6µl/ml for Di-C7-11 PE
1 to 10µl/ml for Di-C13 PE

Results and discussions

Test results

Species/strain	mouse lymphoma L5178Y cells
Metabolic activation	with and without
Test system	all strains/cell types tested
Genotoxicity	negative
Cytotoxicity	
Vehicle controls valid	
Negative controls valid	
Positive controls valid	

Remarks on results including tables and figures

Cells were seeded into a series of tubes at 6 x 106 cells per tube. Mutant

Di-C7 -11 PE: in the absence of activation, 0.75 to 6.0µl/ml induced moderate to high doses. In the presence of a metabolic fraction, 0.125 to 1.5µl/ml resulted in percent r test substance was non-mutagenic in the mouse lymphoma assay with or without me

Di-C13 PE: cytotoxicity ranged from 3.5-21 % at the high dose levels. In the absence increase in mutation frequency. In the presence of a metabolic fraction, 1 to 8µl/ml w of this study the test substance was non-mutagenic in the mouse lymphoma assay w

Overall remarks, attachments

Overall remarks

non-mutagenic in the mouse lymphoma assay

Analogy to Di-C7 -11 PE (a mixture of six phthalate esters consisting of C7, C9, and C11 ester side chains) and Di-C13 PE (CAS No. 119 -06 -2) within the assessment of High Molecular Weight Phthalate Esters.

7.6.2 Genetic toxicity in vivo

Endpoint study record: Key.Analogy 26761-40-0.Genetic toxicity in vivo.MNT

UUID	IUC5-0afd6763-66a9-487c-b03a-0c1820d26770
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 09:28:32 CET
Remarks	

Administrative Data

other:Risk Assessment, EU: REACH

Purpose flag	key study ( ) robust study summary (X) used for classification (X) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliability	2 (reliable with restrictions)
Rationale for reliability	Secondary literature within EU Risk Assessment Report.

Data source

Reference

Reference type	secondary source		
Author	EU	**Year**	2003
Title	EU Risk Assessment Report, DIDP (CAS Nos.: 685151-49-1; 26761-40-0)		
Bibliographic source	Volume 36		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Reference type	study report		
Author	Hazleton Washington	**Year**	1994
Title	Mutagenicity Test on Jayflex DIDP in an in vivo Mouse Micronucleus Assay		
Bibliographic source	Project No 20996 submitted to Exxon Biomedical Sciences		
Testing laboratory	Hazleton Washington	**Report no.**	
Owner company	Hazleton Washington		
Company study no.	20996	**Report date**	

Data access

data published

Materials and methods

Type of genotoxicity

chromosome aberration

Type of study

micronucleus assay

Test guideline

Qualifier	equivalent or similar to
Guideline	OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)
Deviations	no

GLP compliance

yes Hazleton Washington

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	26761-40-0
Identifier	CAS number
Identity	68515-49-1

Details on test material

- DIDP (CAS 26761-40-0 & 68515-49-1)
Jayflex DIDP

Test animals

Species

mouse

Strain

CD-1

Sex

male/female

Administration / exposure

Route of administration

oral: unspecified

Vehicle(s)

- Vehicle(s)/solvent(s) used: corn oil

Duration of treatment / exposure

24, 48 and 72 hours

Frequency of treatment

one application

Post exposure period

24, 48, 72 h

Doses / concentrations

1, 250, 2500 and 5000 mg/kg

Basis nominal conc.

No. of animals per sex per dose

10

Control animals

yes

Positive control(s)

cyclophosphamide
- Doses / concentrations: 80 mg/kg

Examinations

Tissues and cell types examined

bone marrow

Results and discussions

Test results

Sex	male/female
Genotoxicity	negative
Toxicity	no effects
Vehicle controls valid	no data
Negative controls valid	no data
Positive controls valid	yes

Remarks on results including tables and figures

Results:All DIDP dosed groupsappeared normal immediately after dosing and remained heal

Overall remarks, attachments

Overall remarks

DIDP is not clastogenic in a mouse micronucleus assay in vivo.

Analogy to the substance DIDP (CAS 26761 -40 -0 & 68515 -49 -1) within a EU Risk Assessment for DINP.

Applicant's summary and conclusion

Interpretation of results

negative

Endpoint study record: Analogy mix.Genetic toxicity in vivo.MNT

UUID	IUC5-98e00b9c-14bb-442d-8bd7-444410f3fdfb
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 09:28:43 CET
Remarks	

Administrative Data

other:Risk Assessment

Purpose flag	( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliability	4 (not assignable)
Rationale for reliability	Secondary literature within accepted OECD-SIDS.

Data source

Reference

Reference type	secondary source		
Author	OECD	**Year**	2004
Title	OECD SIDS, High Molecular Weight Phthalate Esters (HMWPE)		
Bibliographic source	SIAM 19, Berlin		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	
Reference type	publication		
Author	McKee et al.	**Year**	2000
Title			
Bibliographic source			
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Data access

data published

Materials and methods

Type of genotoxicity

chromosome aberration

Type of study

micronucleus assay

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	288553-12-0
Identifier	CAS number
Identity	68515-48-0
Identifier	CAS number
Identity	26761-40-0
Identifier	CAS number
Identity	68515-49-1

Details on test material

-DINP (CAS 28553-12-0 & 68515-48-0)

-DIDP (CAS 26761-40-0 & 68515-49-1)

Administration / exposure

Route of administration

oral: gavage

Doses / concentrations

up to 2000 (DINP) and 5000 mg/kg (DIDP)

Basis

Results and discussions

Test results

Sex	
Genotoxicity	negative
Toxicity	
Vehicle controls valid	
Negative controls valid	
Positive	

controls
valid

Remarks on results including tables and figures

DINP and DIDP were not active in the mouse micronucleustest.

Overall remarks, attachments

Overall remarks

```
Analogy to the substances
- Di-C7 -11 PE (a mixture of six phthalate esters consisting of C7, C9, and
- Di-C13 PE (CAS 119 -06 -2) within the assessment of High Molecular Weight
```

7.7 Carcinogenicity

Endpoint summary: Carcinogenicity

UUID	IUC5-4acb3ab5-2825-4837-a83e-f54c3658b5aa
Dossier UUID	0
Author	gerstma
Date	2009-10-23 17:57:43 CEST
Remarks	Added EU: REACH data protection flag

Administrative Data

EU: REACH

Discussion

For DINP, the risk assessment concluded that "there was a significant excess of liver neoplasia in rats and mice after oral administration. This is consistent with a peroxisome proliferation mode of action for hepatic tumor induction specific in rodents. It has been established that peroxisome proliferators exhibit their pleiotropic effects to activation of PPARa (peroxisome proliferatoractivated receptor a) and that PPARa 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." For mononuclear cell leukemia, a clearly increased incidence was observed in two studies of DINP conducted with Fisher rats. However, this was considered as a common neoplasm in this strain of rat with no known counterpart in humans. Kidney tumors found in the rat study were regarded as relevant to humans. For DIDP, the risk assessment concluded that a "positive result in the cell transformation test conducted on this chemical was in accordance with those obtained with well-known peroxisome proliferators". Although no carcinogenicity long-term studies have been conducted, the available evidence on DINP and DEHP indicate an increased incidence of hepatocellular tumors in rats related to peroxisome proliferation might be expected for DIDP. As discussed in the risk assessment for DINP, the mechanism of liver tumors would be through peroxisome proliferation and not expected to be a concern in humans.

Endpoint study record: Key.Analogy 85507-79-5.Carcinogenicity

UUID	IUC5-58962a61-318c-460d-a01a-9d0e2ac12c99
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-12-29 16:04:19 CET
Remarks	

Administrative Data

EU: REACH

Purpose flag	key study ( ) robust study summary (X) used for classification (X) used for MSDS
Study result type	read-across from supporting substance (structural analogue or surrogate)
Reliability	2 (reliable with restrictions)
Rationale for reliability	Secondary literature within accepted OECD-SIDS.

Data source

Reference

Reference type	secondary source		
Author	OECD	**Year**	2004
Title	OECD SIDS, High Molecular Weight Phthalate Esters (HMWPE)		
Bibliographic source	SIAM 19, Berlin		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	
Reference type	publication		
Author	Barber E et al.	**Year**	2000
Title	Results of the L5178Y mouse lymphoma assay and the Balb 3T3 cell in vitro transformation assay for eight phthalate esters		
Bibliographic source	J. Appl. Tox. 20 (1), 69-80		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Reference type	study report		
Author	CMA (Chemical Manufacturers Association	**Year**	1985
Title	Evaluation of 1M in the in vitro transformation of BALB/c-3T3 cells assay		
Bibliographic source	Final Report. OTS 0509537. CMA 408526206. CMA, Rosslyn, VA, USA		
Testing laboratory		**Report no.**	OTS 0509537
Owner company	CMA (Chemical Manufacturers Association		
Company study no.		**Report date**	

Data access

data published

Materials and methods

Principles of method if other than guideline

acc. to Clive et al., 1975

GLP compliance

no

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier	CAS number
Identity	68515-48-0
Identifier	CAS number
Identity	28553-12-0
Identifier	CAS number
Identity	68515-49-1
Identifier	CAS number
Identity	117-81-7
Identifier	CAS number
Identity	85507-79-5

Details on test material

-DINP (CAS 68515-48-0 & 28553-12-0)
-DIDP (CAS 68515-49-1)
-DEHP (CAS 117-81-7)
-Di-C11 PE (CAS 85507-79-5)

Test animals

Species

other: BALB/C-3T3 mouse cell line

Strain

Balb/c

Sex

no data

Administration / exposure

Route of administration

other: in medium

Vehicle

no data

Duration of treatment / exposure

3 days

Frequency of treatment

continuously

Doses / concentrations

400-40000 nl/ml

Basis nominal conc.

No. of animals per sex per dose

1-3 (X 10^4) cells

Control animals

yes, concurrent no treatment

Positive control

- 3-methylcholanthrene: 2.5 µg/ml
- methyl-N-intro-N'-nitrosoguanidine: 1.25 µg/ml

Results and discussions

Observations

Remarks on results including tables and figures

Testing was conducted without metabolic activation. Diundecyl phthalate did not significantly increase transformed loci and was considered to be inactive at concentrations at or below its solubility limit in the culture medium. A single, positive result at 12,650 nl/ml in glass, but not in plastic flasks, was inconsistent with the 70% cell survival at this concentration, and was considered uninterpretable. This record reports the results of Trial 5, which was conducted in glass culture vessels.

Overall remarks, attachments

Overall remarks

Analogy to the substances

-DINP (CAS 68515-48-0 & 28553-12-0)

-DIDP (CAS 68515-49-1)

-DEHP (CAS 117-81-7)

-Di-C11 PE (CAS 85507-79-5)

as mentioned in the OECD-SIAP or OECD-SIAR within the assessment of High Molecular Weight Phthalate Esters.

Although the high molecular weight phthalte esters (HMWPE with the exclusion of DINP and DIDP) have not been tested for carcinogenic properties,previous experience with a wide range ofphthalates suggests that high doses might produce liver changes in rodents, butthese are considered not to be relevant to humans and not indicative of a potential human risk.

Three chronic toxicity/carcinogenicity studies of DINP have been conducted; twoin rats and one in the mouse. In the rat studies, the major findings were liver and kidney changes principally related to the induction of peroxisomeproliferation. There was an increase in liver tumors in both male and femalerats and also a small increase in kidney tumors in the male rats. Both of thesetumors are considered to be rat specific and without relevance to humans. In the mouse study, there were liver tumors as well, also the consequence of peroxisomal proliferation, but no tumors of other types. The mouse is less sensitive as compared to the rat.

Endpoint study record: Analogy 26761-40-0.Cho2008.Carcinogenicity

UUID	IUC5-00502e65-dfed-447a-96bd-f1d196327a64
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2010-01-05 19:35:29 CET
Remarks	

Administrative Data

EU: REACH

Purpose flag	supporting study ( ) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliability	4 (not assignable)
Rationale for reliability	Acceptable publication which meets basic scientific principles, however, the dose calculation in the publication is wrong. Further data available based on email correspondence between BASF SE and one of the authors (Cho), refer to any other info at bottom

Data source

Reference

Reference type	publication		
Author	Cho WS et al.	**Year**	2008
Title	Peroxisome proliferator di-isodecyl phthalate has no carcinogenic potential in Fischer 344 rats		
Bibliographic source	Toxicology Letters 178 (2008) 110–116		
Testing laboratory		**Report no.**	
Owner company			
Company study no.		**Report date**	

Data access

data published

Materials and methods

Limit test

no

Principles of method if other than guideline

2 year feeding study

GLP compliance

no data

Test materials

Test material equivalent to submission substance identity

no

Test material identity

Identifier CAS number

Identity 26761-40-0

Details on test material

- Name of test material (as cited in study report): Di-isodecyl phthalate (DIDP)
- Supplier: Sigma–Aldrich Fluka (SAF) Bulk Chemicals (St. Louis, MO)
- Analytical purity: 99.9%

Test animals

Species

rat

Strain

Fischer 344

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS
- Source: Charles River Japan Inc.
- Age at study initiation: ca. 6 weeks
- Housing: two animals per cage
- Diet (e.g. ad libitum): Purina Certified Rodent Chow 5002; ad libitum
- Water (e.g. ad libitum): water; ad libitum
- Acclimation period: 10 - 14 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 22 - 24
- Humidity (%): 50 - 60
- Photoperiod (hrs dark / hrs light): 12 / 12

Administration / exposure

Route of administration

oral: feed

Vehicle

unchanged (no vehicle)

Details on exposure

PREPARATION OF DOSING SOLUTIONS:
DIDP was added to feed on a fixed weight percentage (w/w) basis, and mixed thoroughly to ensure homogeneity.

DIET PREPARATION
- Rate of preparation of diet (frequency): monthly
- Mixing appropriate amounts with (Type of food): fixed weight percentage (w/w) basis
- Storage temperature of food: 4°C

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

The homogeneity and stability of the test chemical in the diet were verified analytically by HPLC.

Duration of treatment / exposure

2 y

Frequency of treatment

daily by feed

Post exposure period

no

Doses / concentrations

400, 2000, 8000 ppm

Basis nominal in diet

No. of animals per sex per dose

52

Control animals

yes, concurrent vehicle

Details on study design

- Dose selection rationale: The maximum tolerated dose of DIDP (9000 ppm) was determined in a preliminary 13-week repeated dose toxicity study (Hong et al., 1999).

Examinations

Observations and examinations performed and frequency

CAGE SIDE OBSERVATIONS: Yes
- Time schedule: twice daily

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: daily

BODY WEIGHT: Yes
- Time schedule for examinations: weekly through week 13, and every 2 weeks thereafter until terminal sacrifice

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Ye
- Compound intake calculated as time-weighted averages from the consumption and body weight gain data: No

FOOD EFFICIENCY:
- Body weight gain in kg/food consumption in kg per unit time X 100 calculated as time-weighted averages from the consumption and body weight gain data: No

OPHTHALMOSCOPIC EXAMINATION: No

HAEMATOLOGY: No

CLINICAL CHEMISTRY: No

URINALYSIS: No

NEUROBEHAVIOURAL EXAMINATION: No

Sacrifice and pathology

GROSS PATHOLOGY: Yes
HISTOPATHOLOGY: Yes

Any other information on materials and methods incl. tables

Following email contacts with Dr. Cho, he provided corrected doses for the study

The mean daily intakes per kg body weights were reported to be 21.9, 110.3, 479.2 mg/kg bw for males

and 22.9, 128.2, 619.6 mg/kg bw for females.

However, the body weights of the dose correction did not fit with the body weights in the publication.

Waiting for letter to the editor of the author to correct the data, therefore, in the meantime, study is val. 4.

Results and discussions

Effect levels

Endpoint	NOAEL
Effect type	carcinogenicity
Effect level	8000
Sex	male/female
Basis for effect level / Remarks	organ weights; histopathology

Observations

Details on results

CLINICAL SIGNS AND MORTALITY

Clinical signs: There were no clinical findings related to DIDP exposure
Mortality:
- 8000 ppm: 33/52 (males), 23/52 (females)
- 2000 ppm: 9/52 (males), 13/52 (females)
- 400 ppm: 14/52 (males), 13/52 (females)
- control: 8/52 (males), 8/52 (females)

BODY WEIGHT
The mean body weights of male and female rats exposed to 8000 ppm were generally less than those of the other treatment groups throughout the study.

FOOD CONSUMPTION AND COMPOUND INTAKE
The average daily doses of DIDP over 2 years for male rats were:
- 8000 ppm: 479.2 mg/kg bw/d (males), 619.6 mg/kg bw/d (females)
- 2000 ppm: 110.3 mg/kg bw/d (males), 128.2 mg/kg bw/d (females)
- 400 ppm: 21.9 mg/kg bw/d (males), 22.9 mg/kg bw/d (females)

ORGAN WEIGHTS
The relative kidney and liver weights of both males and females exposed to 8000 ppm were significantly increased compared to those of the control animals. No treatment-related changes were observed in the relative organ weights for the spleen, testes, ovary, brain, adrenal glands and heart.

HISTOPATHOLOGY:
DIDP produced no treatment-related neoplastic lesions of the liver in either sex.
However, the incidences of mononuclear cell leukemia (MNCL) in the males and females exposed to 8000 ppm were significantly increased compared with the vehicle control, but were within historical ranges in the controls.
- Liver: The incidence of animals with altered cell foci in the liver was significantly decreased in male rats exposed to 2000 and 8000 ppm DIDP, in a dose-dependant manner. The fatty change in the liver decreased in the 8000 ppm exposed males. Oval cell hyperplasia, hypertrophy, necrosis and peliosis of the liver were increased in the 8000 ppm in males compared to the vehicle control. Microgranuloma and spongiosis hepatis of the liver were increased in all the male treatment groups compared to the vehicle control. The incidence of altered cell foci in the liver was generally decreased in the exposed females, with those decreases being significant in the 8000 ppm exposed females compared to the vehicle control. Inflammation of the liver and necrosis were increased in the 400 and 2000 ppm and the 8000 ppm exposed females, respectively. Microgranuloma of the liver was decreased in the 8000 ppm exposed females.
- Adrenal gland: Medullary hyperplasia was increased in the 400 and 2000 ppm exposed males. .
- Spleen: The incidence of extramedullary hematopoiesis was decreased in the 2000 and 8000 ppm exposed females compared to the vehicle control
- Thyroid gland: C-cell hyperplasia of the thyroid gland was decreased in the 2000 ppm exposed males. C-cell hyperplasia was increased in the 400 and 2000 ppm exposed female treatment groups. C-cell adenomas of the thyroid gland were significantly decreased in the male exposed to 400 ppm and the females exposed to 2000 and 8000 ppm compared with the vehicle control, but were within the NTP historical ranges.
- Kidneys: Mineralization and interstitial nephritis were increased in the 8000 ppm exposed males compared to the vehicle control. Hyaline cast, interstitial nephritis and chronic progressive nephropathy were decreased in the 8000 ppm exposed females compared to the vehicle control. Inflammation of the kidney was increased in the 400 and 2000 ppm treatment groups in the exposed females.
- Prostata: Degeneration and inflammation and hyperplasia were increased in the 400ppm and 400 and 2000 ppm in males, respectively.

Other spontaneous lesions and incidences were not related to the treatment, but were within NTP historical ranges (Haseman et al., 1998).

Remarks on results including tables and figures

Final body weights (g) and relative organ weights (mg organ weight/g bw):

		Control	400 ppm	2000 ppm	8000 ppı
Males	Body weight	350.43 ± 46.72	344.19 ± 56.97	357.31 ± 60.80	301.49 ± 68
	Kidney	7.94 ± 1.60	8.63 ± 2.79	8.12 ± 1.53	10.46 ± 2.9
	Liver	31.81 ± 11.26	36.29 ± 20.31	35.04 ± 21.24	44.41 ± 16
	Spleen	6.89 ± 10.26	10.81 ± 17.01	10.31 ± 17.41	13.19 ± 15
	Testis	14.19 ± 5.38	13.53 ± 5.91	14.36 ± 5.16	14.87 ± 8.
Females	Body weight	269.68 ± 36.04	272.68 ± 69.07	268.24 ± 66.46	221.29 ± 50
	Kidney	8.07 ± 1.43	8.51 ± 3.05	8.94 ± 3.72	10.18 ± 2.1
	Liver	31.02 ± 8.33	31.75 ± 11.0	32.14 ± 7.66	46.17 ± 13
	Spleen	5.45 ± 9.67	6.88 ± 9.43	7.48 ± 12.84	11.71 ± 16
	Ovary	0.71 ± 2.47	0.36 ± 0.27	0.57 ± 0.86	0.49 ± 0.5

*Significantly different ($p<0.01$) from the vehicle control group by Williams' or Dunnet

Incidence of neoplastic lesions:

		Control	400 ppm	2000 ppm	8(
Males	All sites examined	50	50	50	
	Mononuclear cell leukemia	10 (20%)	16 (32.0%)	14 (28.0%)	23*
	Thyroid gland	49	49	49	
	C-cell adenoma	10 (20.4%)	4* (8.2%)	11 (22.4%)	6
Males	All sites examined	48	50	49	
	Mononuclear cell leukemia	11 (23.0%)	7 (14.0%)	11 (22.4%)	22
	Thyroid gland	49	47	47	
	C-cell adenoma	8 (16.3%)	5 (10.6%)	2* (4.3%)	0*

*,**Significantly different ($p<0.05$ and $p<0.01$) from the vehicle control group by the p

[a]Tumor incidences in control F344 rats from NTP carcinogenicity studies (Haseman

Incidence of non-neoplastic lesions:

		Control	400 ppm
Number examined		49	48
Adrenal glands	Cortical hyperplasia	3 (6.1%)	2 (4.2%)
	Medullary hyperplasia	0	10** (20.8%)
Kidney	Mineralization	0	1 (2.1%)
	Interstitial nephritis	2 (4.1%)	2 (4.2%)
	Fatty change	4 (8.2%)	6 (12.5%)

Males	Liver	Altered cell foci	27 (55.1%)	19 (39.6%)
		Oval cell hyperplasia	1 (2.0%)	3 (6.3%)
		Hypertrophy	0	0
		Microgranuloma	1 (2.0%)	5* (10.2%)
		Necrosis	3 (6.1%)	7 (14.6%)
		Peliosis	1 (2.0%)	0
		Spongiosis hepatis	0	3* (6.3%)
	Prostate	Degeneration	10 (20.4%)	20* (41.7%)
		Hyperplasia	4 (6.2%)	11* (22.9%)
		Inflammation	5 (10.2%)	7 (14.6%)
	Spleen	Extramedullary hematopoeiesis	9 (18.4%)	5 (10.4%)
		red pulp hyperplasia	3 (6.1%)	1 (2.1%)
	Thyroid gland	C-cell hyperplasia	14 (28.6%)	8 (16.7%)
	Number examined		49	47
Females	Kidney	Hyaline cast	6 (12.2%)	11 (23.4%)
		Inflammation	0	4* (8.5%)
		Interstitial nephritis	6 (12.2%)	3 (6.4%)
		Chronic progressive nephropathy	9 (18.4%)	4 (8.5%)
	Liver	Altered cell foci	31 (63.3%)	26 (55.3%)
		Inflammation	2 (4.1%)	8* (17.0%)
		Microgranuloma	10 (20.4%)	6 (12.8%)
		Necrosis	2 (4.1%)	4 (8.5%)
	Spleen	Extramedullary hematopoeiesis	15 (30.6%)	11 (23.4%)
	Thyroid gland	C-cell hyperplasia	15 (30.6%)	24* (51.1%)

*,**Significantly different (p<0.05 and p<0.01) from the vehicle control group by the p

Overall remarks, attachments

Overall remarks

DIDP was found not to be a liver carcinogen in F344 rats at a dietary level up to 8000 ppm. The relative weights of the liver and kidney

were not accompanied by any histopathologic lesions in those organs. DIDP produced statistically significant increases in MNCL in the 8000-ppm exposed groups, which is a common neoplasm in F344 rats with little or no relevance to humans.

In conclusion, there was no evidence of carcinogenicity in male or female F344 rats exposed to DIDP, with the exception of a marginal increase of MNCL in the 8000 ppm exposed groups, which was not considered a

relevant risk for humans.

7.8 Toxicity to reproduction

Endpoint summary: Toxicity to reproduction

UUID	IUC5-c8f7e57f-572b-4078-b5b8-d2c87870135f
Dossier UUID	0
Author	gerstma
Date	2009-10-23 17:58:45 CEST
Remarks	Added EU: REACH data protection flag

Administrative Data

EU: REACH

Effects on fertility

Short description of key information

Toxicity to reproduction:
- oral: NOAEL = 600 mg(kg bw/d (OECD 416)

Key parameter (optional)

Effect level for oral exposure	NOAEL	**in mg/kg bw/day**	600.000
Effect level for dermal exposure		**in mg/kg bw/day**	
Effect level for inhalation exposure		**in mg/m³ air**	

Discussion

Toxicity to reproduction of di-(2-propylheptyl) phthalate was evaluated in a Two-Generation Reproduction Toxicity Study performed under GLP according guidelines OECD 416, EU Method B.35 and EPA OPPTS 870.3800 (BASF, 2009). The test substance was administered to groups of 25 male and 25 female young Wistar rats via the diet over two parental (F0 and F1) generations with dietary target dosages of 0, 40, 200 and 600 mg/kg bw/day. The test substance concentrations in the diet were adjusted regularly throughout the study to maintain the intended dose levels. It was found, that di-(2-propylheptyl) phthalate neither influenced fertility or reproductive performance in the parental animals, nor viability, sex ratio and sexual development/maturation of offspring, up to the top dose of 600 mg/kg bw/d. Also, neither anogenital distance/anogenital index nor the number and percentage of F1 and F2 male pups having areaolae were influenced in all treated groups. However, the mid and high dose parental animals showed clinical and/or pathological signs of systemic toxicity, while in the high dose

F0 animals and F1 males, intermittent reductions of food consumption and body weights/body weight gain were noted, either during premating, mating, gestation and lactation phases of this study. Furthermore, the rats of both sexes in the F0 as well as in the F1 generation of the high dose group showed a mild anemia. Clinical pathological changes indicated a test substance related effect of the liver cell and bone metabolism beginning in the 200 mg/kg bw/d dose groups in both sexes in the F0 and F1 generation. This was further substantiated by a hepatocellular hypertrophy, which was centrolobular pronounced along with a cytoplasmic eosinophilia, indicative of peroxisome proliferation. Organ weight changes of liver and kidneys as well as corresponding morphological changes in the kidneys, thyroid and pituitary glands are regarded as secondary to the peroxisome proliferation. The F1 and F2 offspring in the high dose group (600 mg/kg bw/d) had significantly reduced body weights and gained also less body weight than the control offspring from day 14 of lactation onwards. Secondary to the reduced body weight gain, lower weights of spleen and thymus were noted in the high dose offspring. Thus, the NOAEL for general, systemic toxicity was determined to be 40 mg/kg bw/d for the F0 and F1 parental rats, based on effects secondary to peroxisome proliferation in the liver, bones, kidneys and thyroid, observed .The NOAEL for fertility and reproductive performance for the F0 and F1 parental rats is 600 mg/kg bw/day, the highest dose tested. The NOAEL for developmental toxicity in the F1 and F2 progeny is 200 mg/kg bw/day, based on slightly decreased pup body weights/pup weight gain in the second third of lactation. Importantly, the developmental effects do not occur in the absence of parental toxicity.

In another study, the structural analogue ditridecyl phthalate (CAS 119-06-2) was tested in a One-generation Study performed according to OECD Guideline 422. 13 male and female Sprague-Dawley rats per dose were treated by gavage with received doses of 0, 10, 50, 250 mg/kg/day in olive oil beginning 14 days before mating until day 3 of lactation (Japan Ministry of Health and Welfare). As result, no adverse effects were observed on copulation, fertility, maintenance of pregnancy, and delivery in any group. A statistically significant decrease in live birth index on postnatal day (PND) 0, possibly due to poor lactation, was observed in the 250 mg/kg group (87.7 in high dose vs 99.6 in controls). Viability of neonates on PND 4 was slightly decreased (not statistically significant) in the 250 mg/kg group. However, there were no adverse effects of ditridecyl phthalate on sex ratio, body weight changes, and morphological appearance of pups. Also, no testicular toxicity was detected in any groups. Thus, the NOELs for reproductive and developmental toxicity were considered to be 250 mg/kg/day in males, 50 mg/kg/day in females, and 250 mg/kg/day in pups, respectively. The same results could be also expected for di-(2-propylheptyl) phthalate due to structural similarities.

Developmental toxicity / teratogenicity

Short description of key information

Developmental toxicity:
- oral: NOAEL = 200 mg/kg bw/d (OECD 414)

Key parameter (optional)

Effect level for oral exposure	NOAEL	**in mg/kg bw/day**	200.000
Effect level for dermal exposure		**in mg/kg bw/day**	
Effect level for inhalation exposure		**in mg/m³ air**	

Discussion

Developmental toxicity of di-(2-propylheptyl) phthalate was analyzed in a Prenatal Developmental Toxicity Study performed under GLP according to guidelines OECD 414 and U.S. EPA Health Effects Test Guidelines OPPTS 870.3700 (BASF, 2003).

Groups of 25 mated female Wistar rats received doses of 0, 40, 200 and 1000 mg/kg bw/d in olive oil by stomach tube on day 6 through day 19 post coitum (p.c.).
No signs of substance-induced maternal toxicity occurred at the low and the mid dose level. However, maternal toxicity was substantiated by clinical signs of discomfort of 5 rats and statistically significant reductions in food consumption, impairments in body weight and body weight gain and reductions in corrected body weight gain at 1000 mg/kg bw. Furthermore, the mean gravid uterus weight was distinctly affected.
Concerning the gestational parameters there was a high rate of resorptions at the top dose, which led to a clearly elevated postimplantation loss value. In contrast, there occurred no substance-induced effects on the gestational parameters at 40 or 200 mg/kg body weight/day. The mean placental and fetal body weights were not affected by treatment, but were similar to or even identical with concurrent control values. Marginal signs of substance induced effects on fetal morphology, but no indications of teratogenicity occurred exclusively at the high dose level. The rates for soft tissue, skeletal and total variations were slightly, but statistically significantly increased. Thus, a borderline effect on fetal morphology in the 1,000 mg/kg fetuses could not be ruled out with certainty, but no indications for selective developmental toxicity were observed up to and including 1,000 mg/kg bw. Based on these clear effects on dams and gestational parameters, but only very mild effects on fetal morphology, the no observed adverse effects level (NOAEL) for maternal and prenatal developmental toxicity was 200 mg/kg body weight/day.

In another unpublished report a prenatal screening study was performed under GLP according to guidelines OECD 414, EU Method B.31 and US EPA OTS 798.4900. Groups of 9 - 10 pregnant female Wistar rats were administered with di-(2-propylheptyl) phthalate at doses of 40, 200 and 1000 mg/kg bw/d in olive oil on day 6 through day 15 post coitum. As results, no signs of maternal toxicity and no signs of developmental toxicity up to and including a dose of 1,000 mg/kg bw/d were found. Also, there were no indications of teratogenic effects which could be causally related to the administration of di-(2-propylheptyl) phthalate. Thus, the no observed adverse effect level (NOAEL) for the maternal and the fetal organism is 1,000 mg/kg body weight/day for this prenatal toxicity screening study in Wistar rats.

Toxicity to reproduction: other studies

Discussion

Justification for classification or non-classification

Due to the observed no adverse effect levels in the Two-Generation Reproduction Toxicity Study and in the Prenatal Developmental Toxicity Study, both performed according to OECD guidelines, no classification according to EU and GHS criteria is necessary

7.8.1 Toxicity to reproduction

Endpoint study record: Key.BASF 70R0183/02087.Toxicity to reproduction.2 Gen

UUID	IUC5-559f7917-b0e0-477d-90d4-538e44c21c9c
Dossier UUID	0
Author	otterr / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-19 16:11:30 CET
Remarks	

Administrative Data

EU: REACH

Purpose flag	key study (X) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliability	1 (reliable without restriction)
Rationale for reliability	Guideline study (OECD)

Data source

Reference

Reference type	study report		
Author	BASF SE	**Year**	2009
Title	PALATINOL 10-P - Two-Generation Reproduction Toxicity Study in Wistar Rats Administration via the diet		
Bibliographic source	Unpublished report		
Testing laboratory	Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany	**Report no.**	70R0183/02087
Owner company	BASF SE		
Company study no.	70R0183/02087	**Report date**	2009-11-02

Data access

data submitter is data owner

Materials and methods

Test type

two-generation study

Limit test

no

Test guideline

Qualifier	according to
Guideline	OECD Guideline 416 (Two-Generation Reproduction Toxicity Study)
Deviations	no
Qualifier	according to
Guideline	EU Method B.35 (Two-Generation Reproduction Toxicity Test)
Deviations	no
Qualifier	according to
Guideline	EPA OPPTS 870.3800 (Reproduction and Fertility Effects)
Deviations	no

GLP compliance

yes (incl. certificate) Experimental Toxicology and Ecology, BASF SE, 67056 Ludwigshafen, Germany

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier	CAS number
Identity	53306-54-0
Identifier	EC number
Identity	258-469-4
Identifier	IUPAC name
Identity	bis(2-propylheptyl) phthalate

Details on test material

- Name of test material (as cited in study report): PALATINOL 10-P
- Test substance No.: 02/0183-2
- Date of production: 09 May 2006
- Physical state: Liquid/ colorless, clear
- Analytical purity: 99.6% peak area-% ((Report Nos.: 06L00115 and 08L00266)
- Lot/batch No.: P94A/06
- Storage condition of test material: Room temperature
- Storage stability: Proven by reanalysis after the in life phase of the study (Report No.: 08L00266)

Test animals

Species

rat

Strain

Wistar

Sex

male/female

Details on test animals and environmental conditions

TEST ANIMALS

- Source: Charles River Laboratories, Research Models and Services, Germany GmbH
- Age at study initiation: (P) 5 wks
- Weight at study initiation: (P) Males: 120.6 - 161.0 g; Females: 110.9 - 145.7 g
- Housing: During the study period, the rats were housed individually in Makrolon type M III cages supplied by Becker & Co., Castrop-Rauxel, Germany (floor area of about 800 cm^2), with the following exceptions: during overnight matings, male and female mating partners were housed together in Makrolon type M III cages; pregnant animals and their litters were housed together until PND 21 (end of lactation). Pregnant females were provided with nesting material (cellulose wadding) toward the end of gestation. For enrichment, wooden gnawing blocks (Typ NGM E-022; supplied by Abedd® Lab. and Vet. Service GmbH, Vienna, Austria) were added.
- Diet (e.g. ad libitum): ground Kliba maintenance diet mouse/rat “GLP” meal, supplied by Provimi Kliba SA, Kaiseraugst, Switzerland; ad libitum
- Water (e.g. ad libitum): Drinking water; ad libitum
- Acclimation period: 7 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20 - 24
- Humidity (%): 30 - 70
- Air changes (per hr): 15x
- Photoperiod (hrs dark / hrs light): 12 / 12

Administration / exposure

Route of administration

oral: feed

Vehicle

unchanged (no vehicle)

Details on exposure

PREPARATION OF DOSING SOLUTIONS:
The test substance was weighed and thoroughly mixed with a small amount of food. Then corresponding amounts of food, depending on the dose group, were added to this premix in order to obtain the desired concentrations. Mixing was carried out for about 10 minutes in a laboratory mixer

DIET PREPARATION
- Rate of preparation of diet (frequency): weekly during premating period for F0 and F1 males and females as well during gestation, lactation and post weaning period for F0 males; once for F0 and F1 females and females during mating period and for F0 and F1 females during gestation, lactation and post weaning period
- Mixing appropriate amounts with (Type of food): ground Kliba maintenance diet mouse/rat “GLP” meal, supplied by Provimi Kliba SA, Kaiseraugst, Switzerland
- Storage temperature of food: room temperature

Details on mating procedure

- M/F ratio per cage: 1/1
- Length of cohabitation: overnight
- Proof of pregnancy: sperm in vaginal smear referred to as day 0 of pregnancy
- Further matings after two unsuccessful attempts: no
- After successful mating each pregnant female was caged (how): pregnant animals and their litters were housed together until PND 21 (end of lactation). Pregnant females were provided with nesting material (cellulose wadding) toward the end of gestation

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

Analytical verifications of the stability of the test substance in the diet for a period of 37 days at room temperature were carried out before the study was initiated.
Homogeneity and concentration control analyses by GC analysis were carried out at the beginning and toward the end of the premating periods. Additionally, at least one analysis of the test substance preparations for female animals was carried out during the gestation and lactation periods. In addition to each sample another one was kept in reserve.

Duration of treatment / exposure

F0: 126 days
F1: 131 days

Frequency of treatment

continuously by diet

Details on study schedule

- F1 parental animals not mated until at least 75 days after selected from the F1 litters.
- Selection of parents from F1 generation when pups were 21 days of age.
- Age at mating of the mated animals in the study: 13 weeks

Doses / concentrations

40, 200, 600 mg/kg bw

Basis nominal in diet

No. of animals per sex per dose

25

Control animals

yes, plain diet

Further details on study design

- Dose selection rationale: y request of the sponsor

Examinations

Parental animals: Observations and examinations

CAGE SIDE OBSERVATIONS: Yes
- Time schedule: at least once daily
- Cage side observations checked in table were included.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: at least once daily

BODY WEIGHT: Yes
- Time schedule for examinations: on the first day of the premating period and then once a week at the same time of the day (in the morning). The F0 and F1 generation parental females were weighed on the day of positive evidence of sperm (GD 0) and on GD 7, 14 and 20. Females with litter were weighed on the day after parturition (PND 1) and on PND 4, 7, 14 and 21. Females were not weighed during pairing until there was positive evidence of sperm in vaginal smears. Females without litter were not weighed during lactation.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study):
- Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Yes
- Compound intake calculated as time-weighted averages from the consumption and body weight gain data: Yes

HAEMATOLOGY: Yes
- Time schedule for collection of blood: a few days before terminal sacrifice of the animals, i.e. after approx. 16 (males) or 18 (females) weeks of treatment; in the morning
- Anaesthetic used for blood collection: Yes, isoflurane
- Animals fasted: No
- How many animals: 10
- Parameters examined: leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelets, differential blood count, prothrombin time

CLINICAL CHEMISTRY: Yes
- Time schedule for collection of blood: a few days before terminal sacrifice of the animals, i.e. after approx. 16 (males) or 18 (females) weeks of treatment; in the morning
- Animals fasted: No
- Anaesthetic used for blood collection: Yes, isoflurane
- How many animals: 10/sex/group
- Parameters examined: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, serum-y-glutamyltransferase, cyanide-insensitive palmitoyl-CoA-oxidation, sodium, potassium, chloride, inorganic phosphate, calcium, urea, creatinine, glucose, total bilirubin, total protein, albumin, globulins, triglycerides, cholesterol, magnesium

Estrous cyclicity (Parental animals)

Estrous cycle length was evaluated by daily analysis of vaginal smear for all F0 and F1 female parental rats for a minimum of 3 weeks prior to mating. Determination was continued throughout the pairing period until the female exhibited evidence of copulation. At necropsy, an additional vaginal smear was examined to determine the stage of estrous cycle for each F0 and F1 female with scheduled sacrifice.

Sperm parameters (Parental animals)

Parameters examined in F0/F1 male parental generations:
testis weight, epididymis weight, sperm count in testes, sperm count in epididymides, sperm motility, sperm morphology

Litter observations

STANDARDISATION OF LITTERS
- Performed on day 4 postpartum: yes
- If yes, maximum of 8 pups/litter (4/sex/litter as nearly as possible); excess pups were killed and discarded.

PARAMETERS EXAMINED
The following parameters were examined in F1 / F2 offspring:
number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross anomalies, weight gain, physical or behavioral abnormalities, organ weights

GROSS EXAMINATION OF DEAD PUPS:
yes, for external and internal abnormalities; possible cause of death was determined for pups born or found dead.

Postmortem examinations (Parental animals)

SACRIFICE
- Male animals: All surviving animal (after weaning of pups the parental animals (F0 and F1) were sacrificed)
- Maternal animals: All surviving animal (after weaning of pups the parental animals (F0 and F1) were sacrificed)

GROSS NECROPSY
- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.

HISTOPATHOLOGY / ORGAN WEIGHTS
The tissues indicated in were prepared for microscopic examination and weighed, respectively:
- Organ weights: Anesthetized animals, Liver, Kidneys, Adrenal glands, Testes, Epididymides, Cauda epididymis, Prostate, Seminal vesicles including coagulation glands, Ovaries, Uterus, Spleen, Brain, Pituitary gland,Thyroid glands (with parathyroid glands)
- Microscopic examination: Vagina, Cervix uteri, Uterus, Ovaries, Oviducts, Left testis, Left epididymis, Seminal vesicles, Coagulation glands, Prostate, Pituitary gland, Adrenal glands, Liver, Kidneys, Spleen, Brain, Thyroids (with parathyroids), All gross lesions

Postmortem examinations (Offspring)

SACRIFICE
- The F1 offspring not selected as parental animals and all F2 offspring were sacrificed at 21 days of age.
- These animals were subjected to postmortem examinations macroscopic and/or microscopic examination) as follows: All culled pups, including stillborn pups and those that died during their rearing period, were subjected to a macroscopic (external and visceral) examination. All pups without any notable findings or abnormalities were discarded after their macroscopic evaluation. Animals with notable findings or abnormalities were further evaluated on a case-by-case basis (e.g., histopathological evaluation or special staining), depending on the findings noted

GROSS NECROPSY
- Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.

HISTOPATHOLOGY / ORGAN WEIGHTS
The tissues indicated in were prepared for microscopic examination and weighed, respectively:
- Organ weights: Liver, Kidneys, Adrenal glands, Testes, Epididymides, Cauda epididymis, Prostate, Seminal vesicles including coagulation glands, Ovaries, Uterus, Spleen, Brain, Pituitary gland,Thyroid glands (with parathyroid glands)
- Microscopic examination: Vagina, Cervix uteri, Uterus, Ovaries, Oviducts, Left testis, Left epididymis, Seminal vesicles, Coagulation glands, Prostate, Pituitary gland, Adrenal glands, Liver, Kidneys, Spleen, Brain, Thyroids (with parathyroids), All gross lesions

Statistics

- Dunnett-test (two sided): Food consumption, body weight and body weight change, estrous cycle duration, number of mating days, duration of gestation, number of implantation sites, postimplantation loss and % postimplantation loss, number of pups delivered per litter, anogenital distance, anogenital index, duration of sexual maturation
- Fisher's Exact Test: Male and female mating indices, male and female fertility indices,

gestation index, females with liveborn pups, females with stillborn pups, females with all stillborn pups, live birth index, pups stillborn, pups died, pups cannibalized, pups sacrificed moribund, viability index, lactation index, number of litters with affected pups at necropsy, sexual maturation data, males with a certain amount of abnormal sperm
- Wilcoxon-Test: Proportions of affected pups per litter with necropsy observations, nipple/ areola anlagen, total spermatids/g testis, total sperm/g cauda epididymides, Sperm motility (%)
- Kruskal-Wallis-Test: Pup organ weights (absolute and relative)

Reproductive indices

- Male mating index (%) = number of males with confirmed mating / number of males placed with females x 100
- Male fertility index (%) = number of males proving their fertility / number of males placed with females x 100
- Female mating index (%) = number of females mated / number of females placed with males x 100
- Female fertility index (%) = number of females pregnant / number of females mated x 100

Offspring viability indices

- Live birth index (%) = number of liveborn pups at birth / total number of pups born x 100
- Postimplantation loss (%) = (number of implantations – number of pups delivered) / number of implantations x 100
- Viability index (%) = number of live pups on day 4 after birth / number of live pups on the day of birth x 100
- Lactation index (%) = number of live pups on day 21 after birth / number of live pups on day 4 after birth x 100

Results and discussions

Effect levels

Endpoint	NOAEL general, systemic toxicity
Generation	P
Sex	male/female
Effect level	40 mg/kg bw/day (nominal)
Basis for effect level / Remarks	peroxisome proliferation in the liver, bones, kidneys and thyroid; body weight; food consumption and compound intake
Endpoint	NOAEL fertility
Generation	P
Sex	male/female
Effect level	600 mg/kg bw/day

Basis for effect level / Remarks	overall effects; organ weights; histopathology; mating index; fertility index
Endpoint	NOAEL fertility
Generation	F1
Sex	male/female
Effect level	600 mg/kg bw/day
Basis for effect level / Remarks	overall effects; organ weights; histopathology; mating index; fertility index
Endpoint	NOAEL
Generation	F1
Sex	male/female
Effect level	200 mg/kg bw/day
Basis for effect level / Remarks	decreased pup body weights/pup weight gain
Endpoint	NOAEL
Generation	F2
Sex	male/female
Effect level	200 mg/kg bw/day
Basis for effect level / Remarks	decreased pup body weights/pup weight gain

Observations: parental animals

Clinical signs (parental animals)

yes

Body weight and food consumption (parental animals)

yes

Test substance intake (parental animals)

yes

Reproductive function: estrous cycle (parental animals)

no effects

Reproductive function: sperm measures (parental animals)

no effects

Reproductive performance (parental animals)

no effects

Organ weights (parental animals)

yes

Gross pathology (parental animals)

no effects

Histopathology (parental animals)

yes

Details on results (parental animals)

CLINICAL SIGNS AND MORTALITY (PARENTAL ANIMALS)
- Mortality: There were no test substance-related mortalities in any of the male and female F0 and F1 parental animals in any of the groups.
- Clinical signs: There were no test substance related clinical findings in the F0 females during the gestation and lactation period for F1 litter. For all dose levels, no clinical signs or changes in general behavior, which may be attributed to the test substance, were detected in male or female F1 generation parental animals. No test substance-related clinical findings were noted in all treated F1 females during the gestation and lactation and period for F2 litter.

BODY WEIGHT AND FOOD CONSUMPTION (PARENTAL ANIMALS)
F0:
- 600 mg/kg bw/d: statistically significantly decreased mean body weights of males during study weeks 7-16 (up to 12%); statistically significantly decreased mean body weight gain of males during study weeks 4-10 and 13-14 (up to 45%); decreased overall body weight of males (-16%; weeks 0 -16); statistically significant lower body weight of females at the end of gestation (GD 20, about 6%) and statistically significantly decreased body weight gain in every gestational week; average decrease of weight gain during gestation (GDs 0-20) in females was about 18%. The body weights of the high dose F0 females remained statistically significant lower (about 8%) than control during the entire lactation period, whereas the lactation body weight gain was comparable to the control group; statistically significant higher food consumption of males during study weeks 3-10 and 12-16; statistically significant lower food consumption of females on GDs 14 -20 (about 7%) during gestation, and statistically significant below control on PNDs 7-14 (about 10%) during lactation
- 200 and 40 mg/kg bw/d: Mean body weights and body weight gain of males were comparable to the control group throughout the entire study. Food consumption of male and female rats was generally comparable to the respective controls throughout the entire study.

F1:
- 600 mg/kg bw: statistically significantly decreased mean body weights of males during study weeks 5-16 (up to 13%); statistically significantly decreased mean body weight gain of males during study weeks 3-11 (up to 31%); reduced overall weight gain of males (-14%; weeks 0-16); sporadically higher (statistically significant during study weeks 4-5) food consumption of males during the study; higher food consumption of female (statistically significant during study weeks 4-5, 6-7, 8-10) for the most part of the study; statistically significant higher food consumption of females on GDs 0 – 7 (about 6%) during gestation
- 200 and 40 mg/kg bw/d: Mean body weights and body weight gain of males were comparable to the control group throughout the entire study. During premating, the mean body weights and body weight gain of all treated parental F1 females (40, 200 and 600 mg/kg bw/d) were comparable to the control group, despite of some sporadical increases/decreases of weight/weight gain in all groups. Also during the gestation and lactation periods body weights and body weight gain of female animals of all treated groups were comparable to the concurrent control group, taking normal biological variability into account. Food consumption of the F1 parental male and female rats was generally comparable to the respective controls throughout the entire study.

TEST SUBSTANCE INTAKE (PARENTAL ANIMALS)
For all test groups the intake of the test substance correlated well with the desired target doses. The actual test substance intake was calculated on the basis of interpolated mean body weights of each test group.

REPRODUCTIVE FUNCTION: ESTROUS CYCLE (PARENTAL ANIMALS)
F0:
The mean estrous cycle duration in the different test groups was similar: 5.4 days in the mid-dose group, 5.6 days in the low-dose group, 6.0 in the control group and 6.1 in the high-dose group.

F1:
The mean estrous cycle duration in the different test groups was similar: 4.0 days in the low-dose group, 4.1 days in the control and 4.2 days in the mid and high-dose groups

REPRODUCTIVE FUNCTION: SPERM MEASURES (PARENTAL ANIMALS)
No treatment-related effects were noted for the sperm parameters, examined at or after the sacrifice of the F0 and F1 parental males.
The number of animals with more than 6.5% abnormal sperm in the F0 high-dose group (600 mg/kg bw/d) was slightly but statistically significant higher. Since the average rate of abnormal sperms as well as the morphology of the testicular tubules were not affected and this parameter was not changed in the F1 generation, this apparent increase is regarded as an incidental finding and biologically not relevant.

REPRODUCTIVE PERFORMANCE (PARENTAL ANIMALS)
- the male mating index was 100% in all groups including the controls for F0 males and 96% in the low-dose group and 100% in the remaining test groups for F1 males.
- the male fertility index ranged between 96% and 100% for F0 males and between 92% and 96% for F1 males without showing any relation to dosing
- the female mating index calculated after the mating period for F1 litter was 100% in all test groups and 100% in test groups 10, 12 and 13 and 96% in test group 11 for the F2 litter
- the fertility index varied between 96% (600 mg/kg bw/d) and 100% for F0 females and 96% in the control, 92% in the mid and high-dose groups and 100% in the low-dose group for F1 females. These values reflect the normal range of biological variation inherent in the strain of rats used for this study. All respective values are within the range of the historical control data of the test facility and do not show any relation to dosing.
- the gestation index was 100% in all groups including controls (0, 40, 200 and 600 mg/kg bw/d), indicating that all pregnant F0 and F1 females had live offsprings.

ORGAN WEIGHTS (PARENTAL ANIMALS)
F0:
- 600 mg/kg bw/d: statistically significant decrease of absolute terminal body weight in males; statistically significant increase of absolute kidney and liver weights; statistically significant increase in absolute cauda epididymis weights, statistically significant decrease of absolute prostate weights statistically significant decrease of absolute seminal vesicle weights and statistically significant decrease of absolute ovary weights were considered as not treatment-related; statistically significant increase of relative kidney weights in males; statistically significant increase of relative liver weights
- 200 mg/kg bw/d: treatment-related effect in the males cannot be excluded; statistically significant increase of absolute kidney and liver weights; statistically significant increase of relative kidney weights in males; statistically significant increase of relative liver weights
- 40 mg/kg bw/d: statistically significant decrease of absolute seminal vesicle weights was considered as not treatment-related; the minimal statistically significant increase of relative liver weights in 40 mg/kg males is disregarded as a treatment-related effect

The statistically significant increase of relative brain weights in 40 mg/kg females and 600

mg/kg males and females, of relative cauda epididymis and epididymides weights in 200 mg/kg and 600 mg/kg males, of relative kidney weights in 40 mg/kg and 600 mg/kg females, of thyroid gland weights in 600 mg/kg females and of testes weights in 600 mg/kg males as well as the statistically significant decrease of seminal vesicle weights in 40 mg/kg males is considered incidental and not treatment-related due to missing histopathological correlates, decrease of absolute terminal body weights and/or missing dose-response relationship
All other mean absolute weight parameters did not show significant differences compared to the control group.

F1:
- 600 mg/kg bw/d: statistically significant decrease of absolute terminal body weight in males; statistically significant increase of absolute kidney weights in males; the statistically significant increase of absolute liver weights in males and females; statistically significant increase of absolute weight of thyroid glands in females; treatment-related effect on the weight development of thyroid glands of males; statistically significant decrease of absolute spleen weights in 600 mg/kg males was considered incidental and not treatment-related; statistically significant increase of relative kidney and liver weights in males and females; statistically significant increase of relative weight of thyroid glands in females; the statistically significant weight increase of brain, cauda epididymis, epididymides, pituitary gland, seminal vesicle, and testes in 600 mg/kg males was considered incidental and not treatment-related due to missing histopathological correlates and explainable by the decrease of terminal body weight.
- 200 mg/kg bw/d: statistically significant increase of absolute kidney weights in males; statistically significant increase of absolute liver weights in males and females; treatment-related effect on the weight development of thyroid glands of males; statistically significant increase of relative kidney weights in males; statistically significant increase of relative liver weights in males and females
- 40 mg/kg bw/d: no treatment-like effect on the weight development of thyroid glands of males

GROSS PATHOLOGY (PARENTAL ANIMALS)
F0:
- 600 mg/kg bw/d: treatment-related liver enlargement of 23 males and 20 females and brown to dark-brown liver discoloration of 15 males;
- 200 mg/kg bw: treatment-related liver enlargement of 2 males

F1:
- 600 mg/kg bw: liver enlargement of 23 males and 14 females and brown to dark-brown liver discoloration of 17 males and 1 female animal
- 200 mg/kg bw: treatment-related liver enlargement of 1 male

All other gross lesions observed in test animals occurred singularly. They are considered to be spontaneous lesions in origin and are not related to treatment.

HISTOPATHOLOGY (PARENTAL ANIMALS)
F0:
- Liver: liver of all male and female animals of 600 mg/kg test group as well as of all male and 2 female animals of the 200 mg/kg test group revealed a minimal (grade 1) to slight (grade 2) diffuse, centrolobular pronounced hepatocytic hypertrophy comprising cytoplasmic eosinophilia and a fine granular structure, indicative for the proliferation within the microsomal compartment (most likely peroxisomes). The liver discoloration was found to be most likely linked to the hepatocellular peroxisome proliferation.

All other findings in the treatment groups were either single observations, or were similar to the control rats in distribution pattern and severity. All of them are considered to be

incidental and/or spontaneous in origin and without any relation to treatment.

F1:
- Liver: The liver of all male and 23 female animals of 600 mg/kg test group as well as of 22 male animals of the 200 mg/kg test group revealed a minimal (grade 1) to slight (grade 2) diffuse, centrolobular pronounced hepatocytic hypertrophy comprising cytoplasmic eosinophilia and a fine granular structure, indicative for the proliferation within the microsomal compartment (most likely peroxisomes).
Several special stains were carried out to elucidate the origin of the macroscopically noted brown discoloration of the liver, which were concluded to be most likely linked to the hepatocellular peroxisome proliferation.
- Kidney: kidneys of 24 male and 6 female animals of 600 mg/kg test group as well as 11 males of 200 mg/kg test group revealed a minimal (grade 1) eosinophilia of proximal tubular epithelial cells. One male animal showed a massive (grade 5) diffuse degeneration of the tubular epithelium in the testis together with a total aspermia and a moderate (grade 3) diffuse atrophy in both epididymides, which corresponded to the gross findings (organ size reduction) and were responsible for the infertility. The female mating partner did not have any histopathological findings.
Another male animal showed, corresponding to the gross lesions, a slight (grade 2) oligospermia in the left epididymis, but the left testis revealed no histopathological findings. The female mating partner did not show any lesions affecting the fertility.
- Thoroid gland: a follicular hypertrophy/hyperplasia was seen in the thyroid glands of 16 males and 18 females of the 600 mg/kg dose group as well as in13 male and 6 female animals of 200 mg/kg dose group. The follicular hypertrophy/hyperplasia in 2 male and 2 female control animals and in 3 male and 3 female animals of the 40 mg/kg dose group are considered incidental and not treatment-related. Altered colloid was seen 9 male and 4 female control animals, 11 males and 5 females of 40 mg/kg group, 21 males and 9 females of 200 mg/kg group and 25 males and 17 females of 600 mg/kg group.
- Pituitary gland: pituitary glands of 7 males of 600 mg/kg dose group revealed a minimal (grade 1) multifocal increase of basophilic cells.

All other findings in the treatment groups were either single observations, or were similar to the control rats in distribution pattern and severity. All of them are considered to be incidental and/or spontaneous in origin and without any relation to treatment.

HEMATOLOGY (PARENTAL ANIMALS)
- 600 mg/kg bw/d: decrease red blood cell counts, hemoglobin values as well as hematocrit values in the F0 and F1 rats of both sexes of the 600 mg/kg bw/d dose group (i.e. after approx. 16-18 weeks of treatment); statistically significant prolonged prothrombin time in the F1 males
-200 mg/kg bw/d: decent but statistically significant decrease of the red blood cell counts in F0 females, but regarded as non-adverse effect; decreased red blood cell counts in the F1 males accompanied by an increase of the MCV and MCH values, which were regarded as incidental.

CLINICAL CHEMISTRY
F0:
- 600 mg/kg bw/d: increase of the alkaline phosphatase activity in females and males; marginal, but statistically significant increase of the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity; bilirubin levels increased in female; decreased globulin values in both sexes; decreased total protein levels in males and females; albumin values were increased in the females (not statistically significant because of a high standard deviation); urea levels were statistically significant increased in the females and there was the same trend in the urea values of the males in this dose group; the triglyceride as well as the cholesterol values in the rats of both sexes were decreased; the calcium levels were decreased in the males
- 200 mg/kg bw/d: increase of the alkaline phosphatase activity in males; marginal, but

statistically significant increase of the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity (for AST not statistically significant in the 200 mg/kg bw/d dose group because of a greater standard deviation); decreased globulin values in both sexes; decreased total protein levels in the males; albumin values were increased in the females; the triglyceride as well as the cholesterol values in the rats of both sexes were decreased; the calcium levels were decreased in the males

F1:
- 600 mg/kg bw/d: increased alkaline phosphatase activities in males and females; increased bilirubin values in females; decreased globulin values in males and females; increased albumin values in males and females; decreased total protein levels in males and females; increased urea values and decreased glucose levels in males; decreased cholesterol and the triglyceride levels in both sexes; decreased calcium levels in males and females; increased inorganic phosphate in males
- 200 mg/kg bw/d: increased alkaline phosphatase activities in males; increased bilirubin values in females; decreased globulin values in males and females; increased albumin values in males and females; decreased total protein levels in males; decreased cholesterol and the triglyceride levels in both sexes; decreased calcium levels in males
- 40 mg/kg bw/d: decreased globulin values in males; the significant decrease of the triglyceride levels in males and low globulin values in the males were seen as non-adverse due to lack of histopathological findings.

Other found changes were marginal, incidental or inconsistent, when compared with the other sex, or lack dose-response relationship. Accordingly, these findings were considered to be of no toxicological significance.

Observations: offspring

Viability (offspring)

no effects

Clinical signs (offspring)

no effects

Body weight (offspring)

yes

Sexual maturation (offspring)

no effects

Organ weights (offspring)

no effects

Gross pathology (offspring)

no effects

Histopathology (offspring)

no effects

Details on results (offspring)

VIABILITY (OFFSPRING)
- The mean number of delivered F1 and F2 pups per dam and the rates of liveborn and stillborn F1 and F2 pups were evenly distributed about the groups. The respective values reflect the normal range of biological variation inherent in the strain used in this study.
- The viability index indicating pup mortality during early lactation (PND 0-4) was 99% in the control and low dose groups for F1 pups. A statistically significant lower viability index in mid dose group (94%) and high dose group (95%) went along with statistically significantly

increased numbers of died and cannibalized pups in the mid and high dose groups.
For F2 pups, the viability index was between PND 0-4 was 98% in test group 13, 99% in control group 10 and 100% in low- and mid dose groups.
- The lactation index for F1 pups indicating pup mortality on PND 4-21 was 100% in control group and low-dose group and 99% in test groups with 200 and 600 mg/kg bw/d.
For F 2 pups, the lactation index was between PND 4-21 varied between 99% (40 mg/kg bw/d) and 100% for the other dose groups.

CLINICAL SIGNS (OFFSPRING)
The F1 generation pups did not display any clinical signs until weaning.
Only one pup (of the high-dose group showed a kinked tail. All other F2 generation pups did not show any clinical signs up to weaning

BODY WEIGHT (OFFSPRING)
Mean body weights of the high-dose F1 male and female pups were statistically significant below control from PND 14 onwards (about 11% on PND 21). Body weight gain was statistically significantly decreased in these pups from PND 4 onwards, the average weight gain during PND 4-21 was about 13% below control.
No test compound-related influence on F1 pup body weights was noted in the low- and mid-dose groups.
Mean body weights of the high-dose F2 male and female pups were statistically significant below control from PND 14 onwards (about 8% on PND 21). Body weight gain was statistically significantly decreased in these pups from PND 7 onwards, the average weight gain during PND 4-21 was about 9% below control.
No test compound-related influence on F2 pup body weights was noted in the low- and mid-dose groups.

SEXUAL MATURATION (OFFSPRING)
- Females: The mean number of days to reach the criterion in the control and 40, 200 and 600 mg/kg bw/d test groups amounted to 30.7, 30.3, 30.2, and 30.9 days, indicating that female sexual maturation was not influenced by the test substance.
- Males: The mean number of days to reach the criterion in the control and 40, 200 and 600 mg/kg bw/d test groups was 41.8, 42.4, 42.2, and 42.2 days, indicating that male sexual maturation was not influenced by the test substance.

ORGAN WEIGHTS (OFFSPRING)
Mean absolute and relative pup organ weights of the F1 pups did not show statistically significant differences to the control group. However, the decreased absolute thymus (-15.8%) and spleen weights (-15.9%) as well as the increased relative brain weights (+10.8%) of the high-dose F1 pups were assessed as secondary to the lower pup body weights in this group. The findings are neither adverse nor toxicologically relevant.
Mean absolute and relative pup organ weights of the F2 pups did not show statistically significant differences to the control group.
The decreased absolute thymus weights (-12.3%) as well as the increased relative brain weights (+9.4%) of the high-dose F2 pups were assessed as secondary to the lower pup body weights in this group. The findings are neither adverse nor toxicologically relevant.

GROSS PATHOLOGY (OFFSPRING)
The number and percentage of male pups having areaolae was not influenced by the test substance when examined on PNDs 12-15.
Neither on anogenital distance nor anogenital index test substance-related effects were noted in all treated F1 offspring (40, 200 and 600 mg/kg bw/d).

HISTOPATHOLOGY (OFFSPRING)
At gross necropsy, a number of common findings were seen in F1 and F2 pups, such as post mortem autolysis, incisors sloped, hemorrhagic thymus, diaphragmatic hernia, dilated

renal pelvis, hemorrhagic testis, small testis and hemorrhagic epididymis. These findings occurred without any relation to dosing and/or can be found in the historical control data at comparable or higher incidences. All these findings were not considered to be associated to the test substance.

Remarks on results including tables and figures

Absolute organ weights:

		Males			
		40 mg/kg bw day	200 mg/kg bw day	600 mg/kg bw day	40 mg/kg bw day
F0	Terminal body weight	99%	96%**	87%**	
	Cauda epididymis	102%	106%	110%**	
	Kidneys	100%	110%**	114%**	
	Liver	101%	121%**	155%**	96%
	Ovaries				98%
	Prostate	103%	100%	91%**	
	Seminal vesicle	92%*	99%	92%*	
F1	Terminal body weight	98%	97%	86%**	
	Kidneys	101%	109%*	107%*	
	Liver	100%	120%**	146%**	105%
	Spleen	101%	98%	84%**	
	Thyroid glands	115%**	119%**	107%*	103%

*: p <= 0.05
**: p <= 0.01

Relative organ weights:

		Males			
		40 mg/kg bw day	200 mg/kg bw day	600 mg/kg bw day	40 mg/kg bw da
F0	Brain	99%	103%	113%**	104%
	Cauda epididymis	104%	111%**	128%**	
	Epididymides	103%	105%*	118%**	
	Kidneys	101%	115%**	132%**	104%
	Liver	103%*	126%**	178%**	98%
	Pituitary gland	100%	100%	100%**	
	Seminal vesicle	93%*	103%	106%	
	Testes	102%	105%	118%**	
	Thyroid glands				111%
F1	Brain	103%	103%	115%**	
	Cauda epididymis	101%	106%	126%**	
	Epididymides	101%	103%	120%**	
	Kidneys	103%	112%**	125%**	101%
	Liver	102%	124%**	171%**	103%

	Pituitary gland	100%	150%	150%**	
	Seminal vesicle	100%	105%	113%**	
	Testes	101%	103%	119%**	
	Thyroid glands	133%**	133%**	133%**	100%

*: p <= 0.05
**: p <= 0.01

7.8.2 Developmental toxicity / teratogenicity

Endpoint study record: Key.BASFAG30R0183/02046.Developmental toxicity / teratogenicity

UUID	IUC5-bfa868d7-3393-45e2-bf34-f720e66ec14c
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 09:29:28 CET
Remarks	

Administrative Data

other:Risk Assessment; Critical study for SIDS endpoint, EU: REACH

Purpose flag	key study (X) robust study summary (X) used for classification (X) used for MSDS
Study result type	experimental result
Reliability	1 (reliable without restriction)
Rationale for reliability	Guideline study (OECD)

Data source

Reference

Reference type	study report		
Author	BASF AG	**Year**	2003
Title	Palatinol 10-P - Prenatal Developmental Toxicity Study in Wistar Rats Oral Administration (Gavage)		
Bibliographic source	Unpublished report		
Testing laboratory	Experimental Toxicology and Ecology, BASF AG	**Report no.**	30R0183/02046, Vol I of III
Owner company	BASF SE		
Company study no.		**Report date**	2003-11-24

Data access

data submitter is data owner

Materials and methods

Limit test

no

Test guideline

Qualifier	according to
Guideline	OECD Guideline 414 (Prenatal Developmental Toxicity Study)

Deviations no

Qualifier according to

Guideline EPA OPPTS 870.3700 (Prenatal Developmental Toxicity Study)

Deviations no

GLP compliance

yes (incl. certificate) Experimental Toxicology and Ecology, BASF AG

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier CAS number

Identity 53306-54-0

Details on test material

- Name of test material (as cited in study report): Palatinol 10-P
- Test substance No.: 02/0 183-1
- Date of production: April 29, 2002
- Physical state: Liquid / colorless
- Analytical purity: 99.2% (Certificate of Analysis, 02L-00204)
- Lot/batch No.: 66A / 02
- Stability under test conditions: Proven by reanalysis after the in-life phase of the study (Analytical Report 03L-00063)
- Storage condition of test material: Room temperature; keep dry

Test animals

Species

rat

Strain

Wistar

Details on test animals and environmental conditions

TEST ANIMALS
- Source: Charles River Laboratories, Germany
- Strain: Wistar (CrlGIxBrlHan:WI)
- Age at study initiation: 70 - 84 at delivery
- Weight at study initiation: 146.3 - 188.6 g
- Housing: single, DK III stainless steel wire mesh cages (Becker, Castrop-Rauxel, Germany)
- Diet (e.g. ad libitum): ground Kliba laboratory diet rat/mouse/hamster, Provimi Kliba SA, Kaiseraugts, Switzerland, ad libitum
- Water (e.g. ad libitum): drinking water; ad libitum
- Acclimation period: between the supply on day 0 and the first administration on gestational day 6

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20 - 24
- Humidity (%): 30 - 70
- Photoperiod (hrs dark / hrs light): 12 / 12

Administration / exposure

Route of administration

oral: gavage

Vehicle

olive oil

Details on exposure

PREPARATION OF DOSING SOLUTIONS:
The test substance solutions in olive 011 Ph.Eur./DAB were prepared at the beginning of the administration period and thereafter at intervals, which took into account the analytical results of the stability verification. For the preparation of the solutions, an appropriate amount of the test substance was weighed in a graduated beakers (depending on the dose group), topped up with olive oil Ph.Eur./DAB and subsequently thoroughly mixed using a magnetic stirrer.

VEHICLE
- Concentration in vehicle: 0.8, 4, 20%
- Amount of vehicle (if gavage): 5 ml/kg bw

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

Analytical verifications of the stability of the test substance in olive oil for a period of at least 7 days at room temperature were carried out by HPLC or GC.

Details on mating procedure

Mating procedure: the animals were mated by the breeder (time-mated) and supplied on day 0 post coitum
- Impregnation procedure: purchased timed pregnant
- Proof of pregnancy: vaginal plug / sperm in vaginal smear referred to as day 0 of pregnancy

Duration of treatment / exposure

day 6 through day 19 of gestation

Frequency of treatment

daily

Duration of test

20 days

Doses / concentrations

40, 200 and 1000 mg/kg bw

Basis nominal conc.

No. of animals per sex per dose

25

Control animals

yes, concurrent vehicle

Examinations

Maternal examinations

CAGE SIDE OBSERVATIONS: Yes
- Time schedule: a check was made twice a day on working days or once a day (Saturday, Sunday or on public holidays) (days 0 - 20 p.c.).
- Cage side observations checked in table were included.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: the animals were examined for clinical symptoms at least once a day, or more often when clinical signs of toxicity were elicited (days 0 - 20 p.c.).

BODY WEIGHT: Yes
- Time schedule for examinations: all animais were weighed on days 0, 1, 3, 6, 8, 10, 13, 15, 17, 19 and 20 p.c.. The body weight change of the animals was caiculated from these results.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study): Yes
- Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Yes
- Compound intake calculated as time-weighted averages from the consumption and body weight gain data: Yes

POST-MORTEM EXAMINATIONS: Yes
- Sacrifice on gestation day 20 p.c.
- Organs examined: uterus, ovaries

Ovaries and uterine content

The ovaries and uterine content was examined after termination: Yes
Examinations included:
- Gravid uterus weight: Yes
- Number of corpora lutea: Yes
- Number of implantations: Yes
- Number of early resorptions: Yes
- Number of late resorptions: Yes
- Other: dead fetuses

Fetal examinations

- External examinations: Yes:
- Soft tissue examinations: Yes: half per litter
- Skeletal examinations: Yes: half per litter
- Head examinations: Yes: half per litter

Statistics

Statistical analysis: Dunnett's test (food consumption, body weight, body weight change, corrected body weight gain, weight of uterus (before opening), weights of fetuses, placentae, corpora lutea, implantations, pre- and post implantation losses, resorptions and live fetuses). KRUSKAL-WALLIS-test (weights of liver, kidneys, spleen). Fisher's exact test (conception rate, mortality of the dams, number of litter with fetal findings). Wilcoxon test (proportion of fetuses with malformations, variations and/or unclassified observation in each litter).

Indices

- The conception rate (in %) was calculated according to the following formula: number of

pregnant animals/number of fertilized animals x 100
- The preimplantation loss (in %) was calculated according to the following formula: (number of corpora lutea - number of implantations) / number of corpora lutea x 100
- The postimplantation loss (in %) was calculated from the following formula: (number of implantations - number of live fetuses) / number of implantations x 100

Any other information on materials and methods incl. tables

Results and discussions

Effect levels

Endpoint	NOAEL
Effect type	embryotoxicity
Effect level	200 mg/kg bw/day
Basis for effect level / Remarks	
Endpoint	NOAEL
Effect type	fetotoxicity
Effect level	200 mg/kg bw/day
Basis for effect level / Remarks	
Endpoint	NOAEL
Effect type	maternal toxicity
Effect level	200 mg/kg bw/day
Basis for effect level / Remarks	
Endpoint	NOAEL
Effect type	teratogenicity
Effect level	1000 mg/kg bw/day
Basis for effect level / Remarks	

Details on maternal toxic effects

MORTALITY
There were no substance-related or spontaneous mortalities in any of the groups.

CLINICAL SIGNS

In total 5 high dose dams showed urine-smeared fur occasionally, predominantly on the last days of the treatment period (days 16 - 20 p.c.).
The clinical finding "urine smeared fur" is a sign of discomfort of the rats and is probably substance-induced. There were no abnormal clinical findings in the other dams of this study.

FOOD CONSUMPTION
- 1000 mg/kg bw/d: mean food consumption was statistically significantly reduced (up to about 32% below the concurrent control value) on treatment days 6 - 13 p.c.. On the following days of the treatment period, food consumption reached or even exceeded control values. If calculated for the entire treatment phase (days 6 - 19 p.c.), food uptake of the 1,000 mg/kg bw/d dams was still about 11 % below the comparable control value. The transient reductions in food consumption at 1,000 mg/kg bw/d were accompanied by corresponding impairments in body weight gain of these dams at initiation of dosing. Therefore, this finding is considered to be substance-induced.
- 40 and 200 mg/kg bw/d: The food consumption of the females was unaffected and did not show any statistically significant or biologically relevant differences in comparison to the controls. This includes the statistically significantly higher food consumption of the mid dose females on treatment days 13 - 15 p.c..

BODY WEIGHT
- 1000 mg/kg bw/d: The mean body weights of the high dose rats were statistically significantly below control values between days 19 - 20 p.c.. On day 20 p.c., the mean body weight of these rats was about 6% below the mean value of the concurrent control females. There was a statistically significant body weight less at 1,000 mg/kg bw/d at initiation of treatment (days 6 - 8 p.c.). This is in-line with the reductions in food intake of these dams during this study phase. Thereafter, weight gains of the high dose dams were generally slightly below corresponding control values without attaining statistical significance. If calculated for the entire treatment period (days 6 - 19 p.c.), however, weight gain of the high dose dams was statistically significantly impaired and about 24% below the respective contral value. A reduction of about 18% occurred at 1,000 mg/kg bw/d, if weight gain was calculated for the total study phase (day 0 - 20 p.c.).
The corrected body weight gain (terminal body weight on day 20 p.c. minus weight of the unopened uterus minus body weight on day 6 p.c.) was distinctly and statistically significantly lower at 1,000 mg/kg bw/d (about 30% below the concurrent control value).
- 40 and 200 mg/kg bw/d: mean body weights, body weight gains and corrected body weight gains were similar to those of the controls. All observable differences in these groups in comparison to the controls during pretreatment and the treatment period are without any biological relevance and reflect the normal variation inherent in the strain of rats used in the present experiment.

UTERUS WEIGHT
- 1000 mg/kg bw/d: the mean gravid uterus weight of the high dose females, was about 19% below the control value, but the difference did not attain statistical significance due to the high standard deviation. The 3 dams of this group which had no live fetuses at all, but only early resorptions had very low uterus weights, whereas the uterus weights of the other dams of this group remained unaffected.
- 40 and 200 mg/kg bw/d: the mean gravid uterus weights were not influenced by the administration of the test substance. The differences between these groups and the control group revealed no dose-dependency and were assessed to be without biological relevance.

REPRODUCTION
- 1000 mg/kg bw/d: a statistically significant increase in resorption rate (especially early ones). Consequently the postimplantation lass value in the top dose was statistically significantly increased (23.1%) and distinctly outside the historical control range (mean value: 6.6%; range: 3.7 - 11.3%). The increased embryo-/fetolethality at 1,000 mg/kg was not equally distributed throughout the dams of this dose group, but was primarily induced

by 3 high dose dams which had no live fetuses at all, but only very early resorptions. Thus, the 3 affected dams were only pregnant by stain and had a postimplantation lass of 100% each, whereas the postimplantation loss values of the other 1,000 mg/kg dams were generally similar to control values.

There were no further substance-related and/or biologically relevant differences between the different test groups in conception rate, in the mean number of corpora lutea and implantation sites or in the values calculated tor the pre- and the postimplantation losses, the number of resorptions and viable fetuses. All respective intergroup differences evinced are considered to be incidental.

NECROPSY
There occurred no substance-related observations at necropsy in any of the dams of all groups. Only the spantaneous occurrence of a bilateral hydrometra was recorded for two high dose rats. Consequently, bath of these rats did not become pregnant.

Embryotoxic / teratogenic effects

yes

Details on embryotoxic / teratogenic effects

WEIGHT
The mean fetal body weights in test groups were not influenced by the test substance administration and were very similar to or even identical with concurrent control values.

SEX DISTRIBUTION
The sex distribution of the fetuses in the test groups 1 - 3 was comparable with that of the control fetuses. The differences observed in comparison to the control were without any biological relevance.

EXTERNAL EXAMINATION
No external malformations or variations were seen in any of the fetuses of test groups, except two unclassified variations which were regarded as isolated and considered to be spontaneous in nature.

SOFT TISSUE EXAMINATION
No soft tissue malformations were recorded in any of the fetuses of all groups.
However, soft tissue variations were detected in each group including the control. Uni- or bilateral dilations of the renal pelvis occasionally in association with uni- or bilaterally dilated ureter(s) were found in fetuses of all groups. The mean percentages of affected fetuses/litter with total soft tissue variations were within the historical control range (4.0 - 22.2%) in test groups (8.5% (control), 9.1% (40 mg/kg bw/d) and 14.8% (200 mg/kg bw/d)), but were above the upper historical control value at 1,000 mg/kg bw/d (26.7%; $p < 0.05$).
No so-called unclassified soft tissue observation (like blood inhibition of kidneys) was recorded in any of the fetuses.

SKELETAL EXAMINATION
Malformations of the skeletons were observed at low incidences in fetuses of the test groups 40 and 1,000 mg/kg bw/d. In total, none out of 115 control fetuses (from 24 litters), 2 out of 105 low dose fetuses (1.9%) in 2 out of 23 litters (8.7%), none out of 114 mid dose fetuses (from 25 litters) and 2 out of 77 high dose fetuses (2.6%) in one of 17 litters (5.9%) showed skeletal malformations. The mean percentages of affected fetuses/litter with skeletal malformations amounted to 0.0, 1.6, 0.0, and 2.4%. The noted skeletal malformations appeared without a clear relation to dosing, without biologically relevant differences between the groups and/or can be found at a comparable frequency in the historical control data
In all groups, signs of skeletal variations with or without involvement of corresponding

cartilaginous structures elicited. The mean percentages of affected fetuses/litter with skeletal variations amounted to 96.0, 95.0, 97.4, and 100% at 0; 40; 200 or 1,000 mg/kg bw/d.
However, two skeletal variations, occurred at statistically significantly rates in the high fetuses (1,000 mg/kg bw/d). The increased occurrence of unossified sternebra and supernumerary rib (without cartilage) were clearly above the upper historical-control values. However, the overall rate of skeletal variations at this dose level was not statistically significantly elevated above the concurrent control value (affected fetuses/litter: 96.0, 95.0, 97.4 and 100.0% in all groups).
Also, unclassified cartliage observations, occurred in all groups including the controls. The mean percentages of affected fetuses/litter with these findings amounted to 38.6, 34.6, 47.2, and 63.5%** at 0; 40; 200 or 1,000 mg/kg bw/d (** = p< 0.01). A toxicological relevance tor these findings could be excluded.

Remarks on results including tables and figures

Maternal examination:

Dose (mg/kg bw/d)	**0**	**40**	**200**	**1000**
Mated females	25	25	25	25
Pregnant females	24	23	25	20
Mortality of dams	0	0	0	0
Pregnant on C-section	24	23	25	20
Clinical symptoms:	-	-	-	+
Food consumption day 6-19 p.c. g	16.9	17.2	17.6	15.1
Mean body weight day 0 (g)	169.2	170.7	173.2	171.9
Mean body weight day 6 (g)	196.9	197.1	201.7	198.3
Mean body weight day19 (g)	265.2	264.4	271.1	250.0*
Mean body weight gain (days 6-19; (g))	68.4	67.4	69.4	51.7**
Uterus weight (g)	49.4	47	48.7	40.2

+ urine smeared fur
*p<0.05; ** p<0.01 (Dunnett test or Kruskal-Wallis and Wilcoxon)

Caesarian section/fetal examination:

Dose (mg/kg bw/d)	**0**	**40**	**200**	**1000**
Corpora lutea (mean)	10.1	9.8	10.5	10.6
Implantation sites (mean)	9.6	9	9.4	9.4
Post-implantation loss (mean %)	6.2	4.2	6.4	23.1**
Dead fetuses/litter (mean %)	0	0	0	0
Resorption sites/litter (mean)	0.5	0.4	0.6	2.2**
Mean No. of live fetuses/litter	9	8.6	8.7	8.6
Mean fetal weights males (g)	3.6	3.6	3.7	3.6
Mean fetal weights females (g)	3.4	3.5	3.5	3.4
% of fetuses with external malformations	0	0.5	0	0
% of fetuses with visceral malformations	0	0	0	0
% of fetuses with skeletal malformations	0	1.9	0	2.6
% of fetuses with external	0	0	0	0

variations				
% of fetuses with visceral variations	8.8	8.7	13	23
% of fetuses with skeletal variations	96	96	97	100

** p<0.01 (Dunnett test or Kruskal-Wallis and Wilcoxon)

Overall remarks, attachments

Overall remarks

Based on the results, which indicate at 1000 mg/kg bw clear effects on dams and gestational parameters, but only very mild effects on fetal morphology, the no observed adverse effects level (NOAEL) for maternal and prenatal developmental toxicity is 200 mg/kg body weight/day.

Endpoint study record: BASFAG10R0110/94013.Developmental toxicity / teratogenicity

UUID	IUC5-56c08920-ba24-4f4c-82ac-a04f1a6764da
Dossier UUID	0
Author	henscho / BASF SE / Ludwigshafen am Rhein / Germany
Date	2009-11-04 14:14:14 CET
Remarks	

Administrative Data

Purpose flag	(X) robust study summary ( ) used for classification ( ) used for MSDS
Study result type	experimental result
Reliability	2 (reliable with restrictions)
Rationale for reliability	Guideline study (OECD)

Data source

Reference

Reference type	study report		
Author	BASF AG	**Year**	1995
Title	Study of the Prenatal Toxicity of DIPROPYLHEPTYLPHTHALATE in Wistar Rats After Oral Administration (Gavage) SCREENING		
Bibliographic source	Unpublished data		
Testing laboratory	Department of Toxicology, BASF AG	**Report no.**	10R0110/94013, Vol I of III
Owner company	BASF SE		
Company study no.		**Report date**	1995-04-03

Data access

data submitter is data owner

Materials and methods

Limit test

no

Test guideline

Qualifier	according to
Guideline	OECD Guideline 414 (Prenatal Developmental Toxicity Study)
Deviations	yes 10 dams instead of 25
Qualifier	according to
Guideline	EU Method B.31 (Prenatal Developmental Toxicity Study)

Deviations yes 10 dams instead of 25

Qualifier equivalent or similar to

Guideline EPA OTS 798.4900 (Prenatal Developmental Toxicity Study)

Deviations yes 10 dams instead of 25

GLP compliance

yes Department of Toxicology, BASF AG

Test materials

Test material equivalent to submission substance identity

yes

Test material identity

Identifier CAS name

Identity 53306-54-0

Details on test material

- Name of test material (as cited in study report): Dipropylheptylphthalate
- Test substance No.: 94/110
- Date of production: May 03, 1994
- Date of bottling: June 03, 1994
- Physical state: liquid/colorless
- Analytical purity: 98.7% (analytical report from July 12, 1994)
- Lot/batch No.: CIW/E - Reg. No. 20596
- Stability under test conditions: The stability off the test substance over the study period was proven by reanalysis
- Storage condition of test material: Room temperature; in tightly sealed container stored in darkness

Test animals

Species

rat

Strain

Wistar

Details on test animals and environmental conditions

TEST ANIMALS
- Source: Dr. K. Thomae GmbH, Biberach, Germany
- Age at study initiation: 60 at delivery; 68 at begin of study
- Weight at study initiation: mean weight approximately 231 g
- Housing: single, DK III stainless steel wire mesh cages (Becker, Castrop-Rauxel, Germany)
- Diet (e.g. ad libitum): ground Kliba laboratory diet rat/mouse/hamster 343 meal, Klingenthalmuehle AG, Kaiseraugts, Switzerland; ad libitum
- Water (e.g. ad libitum): water; ad libitum
- Acclimation period: at least 5 days

ENVIRONMENTAL CONDITIONS
- Temperature (°C): 20 - 24
- Humidity (%): 30 - 70
- Photoperiod (hrs dark / hrs light): 12 / 12

Administration / exposure

Route of administration

oral: gavage

Vehicle

olive oil

Details on exposure

PREPARATION OF DOSING SOLUTIONS:
Each day the test substance solutions were freshly prepared shortly before the test substance was administered. For the preparation of the solutions, an appropriate amount of the test substance was weighed in a volumetric flask, subsequently topped up with olive oil DAB 10 and intensively shaken.

VEHICLE
- Concentration in vehicle: 0.8, 4, 20%
- Amount of vehicle (if gavage): 5 ml/kg bw

Analytical verification of doses or concentrations

yes

Details on analytical verification of doses or concentrations

Analytical investigations to determine the active ingredient content and the homogeneity of the test substance were carried out before the beginning of the study (methods: e.g. IR spectroscopy, gas chromatography and NMR spectroscopy).

Details on mating procedure

- Impregnation procedure: cohoused
- If cohoused:
- M/F ratio per cage: 1/2
- Length of cohabitation: 16.00 hours to about 7.30 hours on the following day
- Further matings after two unsuccessful attempts: no
- Verification of same strain and source of both sexes: yes
- Proof of pregnancy: sperm in vaginal smear referred to as day 0 of pregnancy

Duration of treatment / exposure

day 6 through day 15 of gestation

Frequency of treatment

daily

Duration of test

20 days

Doses / concentrations

40, 200 and 1000 mg/kg bw

Basis nominal conc.

No. of animals per sex per dose

10

Control animals

yes, concurrent vehicle

Further details on study design

- Dose selection rationale: The selection of doses for the present examination was based on the results of several preceding screening studies with different phthalates, which had a similar study design.

Examinations

Maternal examinations

CAGE SIDE OBSERVATIONS: Yes
- Time schedule: check was made twice a day on working days or once a day (Saturday, Sunday or on public holidays; days 0 - 20 p.c.).
- Cage side observations checked in table were included.

DETAILED CLINICAL OBSERVATIONS: Yes
- Time schedule: at least once a day, or more often when clinical signs of toxicity were elicited (days 0 - 20 p.c.).

BODY WEIGHT: Yes
- Time schedule for examinations: on days 0, 1, 3, 6, 8, 10, 13, 15, 17 and 20 p.c.

FOOD CONSUMPTION AND COMPOUND INTAKE (if feeding study): Yes
- Food consumption for each animal determined and mean daily diet consumption calculated as g food/kg body weight/day: Yes
- Compound intake calculated as time-weighted averages from the consumption and body weight gain data: Yes

POST-MORTEM EXAMINATIONS: Yes
- Sacrifice on gestation day 20 p.c.
- Organs examined: liver, kidneys, uterus, ovaries

Ovaries and uterine content

The ovaries and uterine content was examined after termination: Yes
Examinations included:
- Gravid uterus weight: Yes
- Number of corpora lutea: Yes
- Number of implantations: Yes
- Number of early resorptions: Yes
- Number of late resorptions: Yes

Fetal examinations

- External examinations: Yes: all per litter
- Soft tissue examinations: Yes: half per litter
- Skeletal examinations: Yes: half per litter
- Head examinations: Yes: half per litter

Statistics

Dunnett's test (food consumption, body weight, body weight change, corrected body weight gain, liver/kidney weights, weight of uterus (before opening), weights of fetuses, placentae, corpora lutea, implantations, pre- and post implantation losses, resorptions and live fetuses) Fisher's exact test (conception rate, mortality of the dams, number of litter with fetal findings) Wilcoxon test (proportion of fetuses with malformations, variations and/or unclassified observation in each litter

Indices

- The conception rate (in %) was calculated according to the following formula: number of pregnant animals / number of fertilized animals x 100
- The preimplantation loss (in %) was calculated according to the following formula: (number of corpora lutea - number of implantations) / number of corpora lutea x 100
- The postimplantation lass (in %) was calculated from the following formula: (number of implantations - number of live fetuses) / number of implantation x 100

Any other information on materials and methods incl. tables

Results and discussions

Effect levels

Endpoint	NOAEL
Effect type	embryotoxicity
Effect level	1000 mg/kg bw/day
Basis for effect level / Remarks	no effects
Endpoint	NOAEL
Effect type	fetotoxicity
Effect level	1000 mg/kg bw/day
Basis for effect level / Remarks	no effects
Endpoint	NOAEL
Effect type	maternal toxicity
Effect level	1000 mg/kg bw/day
Basis for effect level / Remarks	no effects
Endpoint	NOAEL
Effect type	teratogenicity
Effect level	1000 mg/kg bw/day
Basis for effect level / Remarks	no effects

Maternal toxic effects

no effects

Details on maternal toxic effects

CLINICAL SIGNS
There were no abnormal clinical findings in any dam of anyone group. There were no mortalities in any of the groups.

FOOD CONSUMPTION
The food consumption of the female rats of all test groups did not show any differences of biological relevance if compared to the controls. All food consumption values calculated are within the range of biological variation.

BODY WEIGHT AND BODY WEIGHT GAIN
Body weights and body weight gains of the dams of all test groups were similar to those of the controls. All observable differences between these groups and the control group are without any biological relevance; this includes the statistically significantly higher weight gain of the 40 mg/kg bw/d dams between days 13 - 15 p.c.
The results of the corrected body weight gain (terminal body weight an day 20 p.c. minus weight of the uterus before it was opened minus body weight an day 6 p.c.) of all substance-treated groups did not show any differences of biological relevance if compared to the controls.

ORGAN WEIGHTS
The uterus weights of the animals of all test groups were not influenced by the administration of the test substance. The differences between these groups and the control group are without biological relevance and do not show a clear relation to dosing.
Absolute and relative liver and kidney weights were not influenced by the administration of the test substance. The differences between the groups are without biological relevance and do not show a clear relation to dosing.

NECROPSY
Single animals of all groups including the controls showed lungs with edema and/or marginal emphysema; these findings, which showed no relation to dosing, have to be related to the sacrifice of the animals.

REPRODUCTION
There were no substance-related and/or biologically relevant differences between the groups in conception rate, in the mean number of corpora lutea and implantation sites or in the values calculated for the pre- and the postimplantation losses, the number of resorptions and viable fetuses. The differences evident are considered to be incidental and within the normal range of deviations for animals of this strain and age.

Embryotoxic / teratogenic effects

no effects

Details on embryotoxic / teratogenic effects

SEX DISTRIBUTION
The sex distribution of the fetuses in all test groups was comparable with the control fetuses. The differences observed in comparison to the control are without any biological relevance.

WEIGHT OF PLACENTAE
The mean placental weights in all test groups were not influenced by the test substance administration and were similar to the control values.

WEIGHT OF FETUSES
The mean fetal body weights in all test groups were not influenced by the test substance administration and were similar to the control values.

EXTERNAL EXAMINATION
The external examination revealed only one high dose fetus with an external malformation (microphthalmia of the left eye), which was considered to be spontaneous in nature and not related to the test substance administration.
The external examination of the fetuses revealed no variations in any group.
Only one so-called unclassified observation (placenta necrobiotic) was seen in one out of 153 (0.7%) high dose fetuses (in one out of 10 litters (10%). This placental finding was not associated with treatment, because it appears also from time to time in control fetuses of the rat strain used

SOFT TISSUE EXAMINATION
The examination of the organs off the fetuses revealed only one type of soft tissue malformation in fetuses of the control and the low dose group:
Dextrocardia was seen in 2 out of 61 examined fetuses (3.3%) from 2 out of 10 litters (20%) of the control group and in 2 out of 62 examined fetuses (3.2%) in 2 out of 9 litters (22% of test group 40 mg/kg bw/d). No soft tissue malformations occurred at 200 and 1,000 mg/kg body weight/day.
Because no relation to dosing is given and because dextrocardia is also present at a low incidence in the historical control data, the recorded visceral finding is considered to be spontaneous in nature.
Soft tissue variations (dilated renal pelvis and/or hydraureter) were detected in all groups without any statistically significant and/or biologically relevant differences between the groups.
No so-called unclassified observation (like bloody inhibition of kidneys) was recorded during the soft tissue observation.

SKELETAL EXAMINATIO
All skeletal malformations (thoracic vertebral body/bodies dumbbell-shaped (asymmetrical); lumbar vertebra absent) and/or the sternum (sternebrae) bipartite, ossification centers dislocated) occurred without any statistically significant differences between the substance-treated groups and the concurrent control group and did not show any relation to dosing.
The skeletal variations elicited were related to the vertebral column (accessory thoracic vertebra), the sternum (sternebrae of irregular shape or bipartite; accessory sternebra) and/or the ribs (shortened 13th, accessory 14th or rudimentary cervical ribs).
All except one of the skeletal variations recorded appeared without any statistically significant differences between the substance-treated groups and the concurrent control group and/or without a clear dose-response relationship.
However, the accessory 14th rib affected most frequently the high dose fetuses, was also not assessed as a treatment-related effect, but is considered to be spontaneous in nature and without biological relevance.
Regarding skeletal retardation, an increased occurrence of incompletely ossified thoracic vertebral body/bodies was observed in the intermediate (200 mg/kg bw/d) group and the mean percentage of affected fetuses/litter with dumbbell shaped thoracic vertebral body/bodies (symmetrical) was statistically significantly increased at the lowest dose tested (40 mg/kg bw/d). However, due to a missing dose-response relationship, it was not associated with treatment.

Remarks on results including tables and figures

Maternal examination:

Dose (mg/kg bw/d)	**0**	**40**	**20**	**1000**
Mated females	10	10	10	10
Pregnant females	10	9	10	10
Mortality of dams	0	0	0	0
Pregnant on C-section	10	9	10	10

Clinical symptoms	-	-	-	-
Food consumption (day 6-21 p.c.; g)	22.5	23.4	23.1	24
Mean body weight day 0 (g)	228.4	236.5	232.8	227.6
Mean body weight day 6 (g)	257.2	264.8	260.1	260.1
Mean body weight day 15 (g)	303.6	314.1	308.2	313
Mean body weight day 20 (g)	376.4	387.4	380.9	393.1
Mean body gain days 6-21 p.c. (g)	46.4	49.4	48.1	52.9
Uterus weight (g)	72.7	78.8	75.5	87.7
Fetal examination:				
Dose (mg/kg bw/d)	**0**	**40**	**20**	**1000**
Corpora lutea	15.1	16	15.6	16.7
Implantation sites	14.2	14.9	13.8	16.4
% post-implantation loss	9.2	7.2	3.8	6.5
% dead fetuses/litter	0	0	0	0
Resorption sites/litter	1.3	1	0.6	1.1
Mean no. Live fetuses/litter	12.9	13.9	13.2	15.3
Mean fetal weights of males (g)	3.9	4	4	4
Mean fetal weights of females (g)	3.7	3.8	3.7	3.8
% fetuses with external malformations	0	0	0	1
% fetuses with visceral malformations	3.3	3.2	0	0
% fetuses with skeletal malformations	8.8	4.8	1.4	3.7
% fetuses with external variations	0	0	0	0
% fetuses with visceral variations	15	19	22	21
% fetuses with skeletal variations	56	33	59	51

Overall remarks, attachments

Overall remarks

In this screening study Dipropylheptylphthalate caused no signs of maternal toxicity and no signs of developmental toxicity up to the highest investigated dose level of 1000 mg/kg bw. No indication for any teratogenicity was observed. The no observed adverse effect level (NOAEL) for the maternal and fetal organism was 1000 mg/kg bw.

Reference substance: bis(2-propylheptyl) phthalate

UUID ECB5-7090053a-8460-4fe1-8bb5-9f9708ae6219
Dossier UUID 0
Author gerstma
Date 2009-10-26 12:22:09 CET
Remarks Added EU: REACH data protection flag

General information

Reference substance name bis(2-propylheptyl) phthalate

EC inventory

EC number 258-469-4 **CAS number** 53306-54-0
EC name bis(2-propylheptyl) phthalate
Molecular formula C28H46O4

Reference substance information

CAS information

CAS number 53306-54-0
CAS name 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester

IUPAC name

IUPAC name bis(2-propylheptyl) phthalate

Synonyms

Name 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester
Name 1,2-Benzenedicarboxylic acid, bis(2-propylheptyl) ester

USEPA Category: Esters

Molecular and structural information

EU: REACH

Molecular formula C28H46O4
Molecular weight range 446.6624
SMILES notation CCCCCC(CCC)COC(=O)c1ccccc1C(=O)OCC(CCC)CCCCC
InChI InChI=1/C28H46O4/c1-5-9-11-17-23(15-7-3)21-31-27(29)25-19-13-14-20-26(25)28(30)32-22-24(16-8-4)18-12-10-6-2/h13-14,19-20,23-24H,5-12,15-18,21-22H2,1-4H3
Structural formula

Legal entity: BASF SE

UUID	IUC4-fa6b5320-73c6-367e-9073-49dcfd348866
Dossier UUID	0
Author	gerstma
Date	2009-10-22 10:48:00 CEST
Remarks	Added EU: REACH data protection flag

General information

Legal entity name	BASF SE
Legal entity type	company

Identifiers

Legal entity identifiers

EU: REACH

Identifier type	DUNS
ID	315000554

EU: REACH

Identifier type	VAT
ID	DE149145247

Contact information

Contact address

Address flags	**EU: REACH**
Address	Carl-Bosch-Str. 38
Postal code	67056
Town	Ludwigshafen am Rhein
Region / State	Rheinland-Pfalz
Country	Germany
Phone	+49-621-60-73224
E-mail	reach@basf.com
Web site	http://www.basf.com

Contact persons

Person flags	**EU: REACH**
Organisation	BASF SE
Department	GUP/CR - Z570

First name	Contact
Last name	REACH
Phone	+49-621-60-73224
Fax	+49-621-60-6673224
E-mail	reach@basf.com
Address	Carl-Bosch-Str. 38
Postal code	67056
Town	Ludwigshafen am Rhein
Region / State	Rheinland-Pfalz
Country	Germany

Sites

Site Ludwigshafen