Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to

Di-isodecylphthalate (DIDP) for use in food contact materials

Question N° EFSA-Q-2003-195

Adopted on 30 July 2005

SUMMARY

The Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) has been asked to re-evaluate di-isodecylphthalate for use in the manufacture of food contact materials.

There are two different di "isodecyl" phthalate products with different CAS numbers (68515-49-1 and 26761-40-0). According to the European Council for Plasticisers and Intermediates (ECPI) these two products are prepared essentially from the same starting materials, through an identical olefin oligomerisation process and through similar oxo alcohol manufacturing and phthalate esterification processes.
The two phthalates are considered fully interchangeable within their whole range of the market end uses. Therefore, in this document they are considered together.

Previously, a group Tolerable Daily Intake (g-TDI) of 0.15 mg/kg bw (with di-isononylphthalate – (DINP)) was set by the Scientific Committee for Food (SCF), based on the endpoint of peroxisome proliferation in rodent liver. There is now a scientific consensus that liver peroxisome proliferation in rodents is not relevant for human risk assessment. The usual critical effects of phthalates relate to liver, testicular and reproduction toxicities. From the several studies available on DIDP, the critical observations were as follows:

There is no indication of effects on reproductive organs from histological observation in repeated dose toxicity studies.

In a recent two-generation study in rats, the F2 offspring survival was decreased. Based on this effect, a no observed adverse effect level (NOAEL) of 33 mg/kg bw/day could be established.

In a 13-week oral study in dogs, liver changes were seen at higher dose levels with a lowest observed adverse effect level (LOAEL) of 77 mg/kg bw/day and 88 mg/kg bw/day for male and female dogs respectively. The Panel concluded that the NOAEL of 15 mg/kg bw/day from this study should be used in the risk assessment.

Based on the liver effects in dogs (a species considered as a non-sensitive species to peroxisome proliferation) with a NOAEL of 15 mg/kg bw/day, and on a decrease of F2 offspring survival with a NOAEL of 33 mg/kg bw/day, a lowest overall NOAEL of 15 mg/kg bw/day has been considered. Making use of this NOAEL and of an uncertainty factor of 100, a TDI of 0.15 mg/kg bw is derived.

The limited data available on DIDP concentration in foods and diets in UK (1996, 1998) and Denmark (2003) were used to provide an estimation of the dietary exposure. In the UK, potential exposure to DIDP from dietary sources was based on the method detection limit and estimated to be less than 0.17 µg/kg bw/day. For newborns (0-6 months) and for infants (>6 months), the potential exposure to DIDP derived from infant formulae consumption corresponded to 2.4 µg/kg bw/day and 1.8 µg/kg bw/day respectively.

A Danish DIDP total oral exposure was reported recently and was estimated to be 3 µg/kg bw/day for adults. Higher values for total oral exposure (210, 53 and 7 µg/kg bw/day) were reported for infants (6-12 months), children (1-6 years) and children (7-14 years), respectively. However the two highest values for young children, derived mainly from the contribution of the estimated oral exposure related to toys that is included in the above values. DIDP use in toys is provisionally banned in the EU since 1999. Furthermore, the computer modeling program (EUSES) which was used for these intake estimates is a conservative one and the obtained values are not representative of the possible exposure via food contact materials. However, the value of 7 µg/kg bw/day from this study has been taken as a worst case estimate of dietary exposure to DIDP.

The Panel noted that the above estimated exposure via the diet of around 7 µg/kg bw/day is well below the TDI. However, there are some indications that DIDP levels in food may be increasing in recent years, and so, more up-to-date estimations of exposure from the diet are desirable.

The Panel noted also that DIDP and DINP (phthalic acid, diester with primary saturated C8-C10 branched alcohols, C9 rich, CAS n° 28553-12-0 and 68515-48-0, PM/REF 75100) are mixtures that overlap chemically with each other and cannot analytically be distinguished clearly if present in a mixture. For this reason, it is proposed that for DINP and DIDP a group restriction is established for migration from food contact materials.

KEY WORDS：

1,2-benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich (CAS n° 68515-49-1); di-''isodecyl'' phthalate (CAS N° 26761-40-0); di-isodecylphthalate; REF No. 75105, food contact materials

BACKGROUND

DIDP may be present in food, either due to migration from food contact materials containing DIDP or due to its widespread presence as an environmental contaminant which can be found in air, water, soil and food. DIDP was evaluated by the Scientific Committee for Food (SCF) in 1999 when a group TDI (with DINP) for use in food contact materials was established based on the then most sensitive end-point of peroxisome proliferation in rodent liver (SCF, 1999). There is a scientific consensus that liver peroxisome proliferation in rodents is not a relevant endpoint for human risk assessment (IARC, 1995). The Panel has therefore been asked to re-evaluate DIDP for use in food contact materials.

TERMS OF REFERENCE

The Commission asks EFSA to re-evaluate di-isodecylphthalate (DIDP) for use in the manufacture of food contact materials.

ASSESSMENT

1. Chemistry

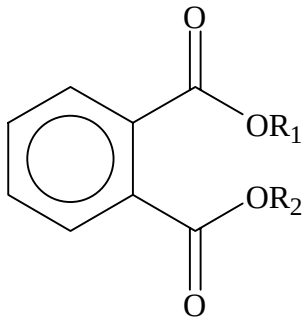
Identification of the substance

There are two different di "isodecyl" phthalate products with different CAS numbers (68515-49-1 and 26761-40-0). According to specific information from the European Council for Plasticisers and Intermediates (ECPI, 1996) these two products are prepared essentially from the same starting material, through an identical olefin oligomerisation process and through similar oxo alcohol manufacturing and phthalate esterification processes.
The two phthalates are considered fully interchangeable within their whole range of the market end uses.

CAS	68515-49-1	26761-40-0
EINECS-Nr	271-091-4	247-977-1
Substance name (IUPAC Name)	1,2-benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich	1,2-benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich (di-''isodecyl'' phthalate)
Molecular formula	$C_{28}H_{46}O_4$ (average)	
Molecular weight	446.68 (assuming the above average molecular formula)	

FCM Ref N°75105

Structural formula:



where R1 and R2 = C9-C11, C10 rich, linear and branched

The correct structures can only be estimated. Based on nonene (CAS 97593-01-6) isomer distribution analysis and 1H-NMR analysis of isodecyl alcohol, an estimation of key isomeric structures of isodecylalcohol, and hence of DIDP were provided by ECPI (1998).

Longest chain (estimates)	DIDP (CAS 68515-49-1 & CAS 26761-40-0)	Best estimated content (%)

C7	tri-methylheptanols	0-10
C8	di-methyloctanols	70-80
C9	methylnonanols	0-10
C10	n-decanol	0

Purity/impurities, additives

Phthalates are produced with a high degree of purity (> 99.5%), in terms of ester content. Trace impurities have been summarised from producers' data.

Diisodecyl ether and Isodecyl benzoate	0.02 - 0.1% w/w
Isodecyl alcohol	0.01 - 0.05% w/w
Water	max. 0.1% w/w

Physico-chemical properties

Property	Value
Melting point	-53 to -39°C (av. -45°C)
Boiling point	> 400°C
Density	0.966 at 20°C
Vapour pressure	$5.1.10^{-5}$ Pa at 25°C
Water solubility	0.2 µg/l at 20°C
Log Kow	8.8

2. Use

1,2-benzenedicarboxylic acid, di-C9-C11-branched alkyl esters, C10-rich (CAS n° 68515-49-1, EINECS n° 271-091-4) / di-''isodecyl'' phthalate (CAS n° 26761-40-0, EINECS n° 247-977-1) is mainly used as plasticiser in PVC.

3. Exposure via food

No data on the levels of DIDP in food in the EU attributable to migration from food contact materials have been submitted by the industry.

In 1996, MAFF's Food Safety Directorate carried out a survey of the levels of DIDP and total phthalates in samples of composite fatty foods (MAFF 1996a). DIDP was not detected in the conditions of analysis (limit of detection = 0.01 mg/kg of food). Based on the detection limit, and

assuming a food intake per day of 1 kg for an adult of 60 kg, the potential daily exposure to DIDP from food would be < 0.17 µg/kg bw/day.
For newborns (0-6 months) and for infants (>6 months), the potential exposure to DIDP derived from infant formulae consumption, based on the detection limit, corresponds to 2.4 µg/kg bw/day and 1.8 µg/kg bw/day respectively (MAFF, 1996b and 1998).

A Danish DIDP total oral exposure was reported recently (Müller et al, 2003) and was estimated to be 3 µg/kg bw/day for adults. Higher values for total oral exposure (210, 53 and 7 µg/kg bw/day) were reported for infants (6-12 months), children (1-6 years) and children (7-14 years), respectively. But these two highest values for young children derive mainly from the contribution due to the estimated oral exposure related to toys that is included in the above values. DIDP use in toys is provisionally banned in the EU since 1999 (Commission Decision, 1999 and 2004). Furthermore, the computer modeling program (EUSES) which has been used for these intake estimates is a conservative one and the obtained values are not representative of the possible exposure via food contact materials. However, the value of 7 µg/kg bw/day from this study has been taken as a worst case estimate of dietary exposure to DIDP.

There are some indications that DIDP levels in food are increasing in recent years, and so, more updated estimations of exposure from the diet are desirable.

4. Toxicological evaluation

Introduction

The Panel did not carry out a new extensive risk assessment but took cognisance of the previous evaluations by the SCF and in particular considered the more recent DIDP Risk Assessment Report (RAR), prepared for the European Union Existing Substances Regulation, 793/93, 2001 (Annex 1), and the comments of the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) on this RAR (Annex 2), in order to determine the most significant toxicological end-point for risk assessment. Based on this information, the Panel focused on the most sensitive toxicological end-points for the evaluation of DIDP.

The SCF expressed its opinion on DIDP in December 1999 (SCF, 1999) based on the following statement in the safety data sheet:

> "The liver was identified as the target organ following oral administration of DIDP in rats and dogs. A dose-dependent increase in absolute liver weight was found. A NOAEL of 15 mg/kg bw/day could be derived from these studies, based on liver effects following repeated oral exposure.
> Making use of an uncertainty factor of 100 (10 for intraspecies and 10 for interspecies), a TDI of 0.15 mg/kg bw/day could be allocated to DIDP.
>
> DIDP and DINP (phthalic acid, diester with primary saturated C8-C10 branched alcohols, C9 rich and di-"isononyl"phthalate) being mixtures overlapping chemically each other it is decided to establish a group restriction of 9 mg/kg food, together with DINP (CAS n° 28553-12-0 and 68515-48-0, PM/REF. 75100)."

Studies considered by the AFC Panel

The following studies on genotoxicity, carcinogenicity, liver toxicity, reproduction and development toxicities considered by the Panel for the determination of a NOAEL which could be used as a basis for a TDI calculation are summarized below. Further details on these studies are given in Annex 1

(Risk Assessment Report) and Annex 2 (CSTEE opinion). Long-term studies on carcinogenicity for DIDP are not available.

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

Repeated-dose toxicity in rats produced peroxisome proliferation-related liver and thyroid effects accompanied by increases in liver weight (Hazelton Laboratories, 1968a, BASF, 1969 a and b). A NOAEL of 60 mg/kg bw/day was identified in the latter study based on increased relative liver weight in female rats. This study is not relevant for the determination of a TDI since the NOAEL was based on peroxisome proliferation.

In a 13-week oral study in dogs using dose levels of 0.05, 0.3 and 1% in the diet, liver changes (swollen and vacuolated hepatocytes and dose-related increases in liver weight increases) were seen at the two higher dose levels (Hazleton Laboratories, 1968b). A NOAEL of 15 mg/kg bw/day was identified by the study authors and by the RAR. The fact that dogs are considered to be non-responsive or refractory to peroxisome proliferation could indicate that minor liver damage found in this species occurred by a mechanism different to peroxisome proliferation. The Panel noted that the RAR and CSTEE opinions commented that the small number of animals in the study precluded statistical analysis and that the validity of this NOAEL may be in question. The Panel also noted that the NTP-CERHR Expert Panel concluded that it was not possible to derive a NOAEL for this study, and that a LOAEL of 77 mg/kg bw/day and 88 mg/kg bw/day for male and female dogs, respectively, should be considered (CSTEE opinion).

There is no indication of effects on reproductive organ from histological observation in repeated dose toxicity studies in rats (BASF, 1969b and 1995; Hazelton, 1968b) and in dogs (Hazelton, 1968b).

With respect to reproductive toxicity, decreases in survival indices were observed consistently in 2 two-generation studies with rats (Exxon Biomedical Sciences, 1997b; 2000). NOAELs of 38-44 and 52-114 mg/kg bw/day during pregnancy and lactation were identified for reproductive toxicity by the study authors. In the more recent two-generation study in rats (Exxon Biomedical Sciences, 2000), the F2 offspring survival was decreased. A NOAEL of 33 mg/kg bw/day (lowest estimated dose for 0.06% DIDP in the diet) could be derived for this effect.

The results of the one- and two-generation studies showed that DIDP did not affect fertility in rats.

With respect to developmental effects, skeletal variations (including rudimentary lumbar ribs and supernumerary cervical ribs) were observed in developmental studies in rats at 1,000 mg/kg bw/day concurrently with slight signs of maternal toxicity. A NOAEL of 500 mg/kg bw/day for maternal toxicity and a NOAEL of 100 mg/kg bw/day for developmental effects were established in the two-generation rat study (Exxon Biomedical Sciences, 1997b; 2000).

CONCLUSIONS

Based on all the available toxicological evidence, the Panel concluded that effects on liver, reproduction and development are the end-points on which to base the risk assessment. Previous reviews on phthalates have identified as pivotal several rat reproduction studies conducted in the last decade, which gave NOAELs or LOAELs in the region of 15-150 mg/kg bw/day.

There is no indication of effects on reproductive organs from histological observation in repeated dose toxicity studies (BASF, 1969b; Hazelton, 1968b).

In a recent two-generation study in rats (Exxon Biomedical Sciences, 2000), the F2 offspring survival was decreased. Based on this effect, a NOAEL of 33 mg/kg bw/day could be derived.

In a 13-week oral study in dogs, liver changes were seen at higher dose levels with a LOAEL of 77 mg/kg bw/day and 88 mg/kg bw/day for male and female dogs, respectively. The Panel concluded that the NOAEL of 15 mg/kg bw/day from this study should be used in the risk assessment.

Based on the liver effects in dogs (a species considered as a non-sensitive species to peroxisome proliferation), with a NOAEL of 15 mg/kg bw/day and on a decrease of F2 offspring survival with a NOAEL of 33 mg/kg bw/day, a lowest overall NOAEL of 15 mg/kg bw/day has been considered. Making use of this NOAEL and of an uncertainty factor of 100, a TDI of 0.15 mg/kg bw is derived.

The limited data available on DIDP concentration in foods and diets in UK (1996, 1998) and Denmark (2003) were used to provide an estimation of the dietary exposure. In the UK, potential exposure to DIDP from dietary sources was based on the method detection limit and estimated to be less than 0.17 µg/kg bw/day. For newborns (0-6 months) and for infants (>6 months), the potential exposure to DIDP derived from infant formulae consumption corresponds to 2.4 µg/kg bw/day and 1.8 µg/kg bw/day respectively,

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The Panel noted that the above estimated exposure via the diet of around 7 µg/kg bw/day is well below the TDI. However, there are some indications that DIDP levels in food have increased in recent years, and so, more up-to-date estimations of exposure from the diet are desirable.

The Panel noted also that DIDP and DINP (phthalic acid, diester with primary saturated C8-C10 branched alcohols, C9 rich, CAS n° 28553-12-0 and 68515-48-0, PM/REF 75100) are mixtures that overlap chemically with each other and cannot analytically be distinguished clearly if present in a mixture. For this reason, it is proposed that for DINP and DIDP a group restriction is established for migration from food contact materials.

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ANNEX 1

Extracts from the Risk Assessment Report on DIDP
Consolidated Final Report (dated May 2001)

Summary on mutagenicity and carcinogenicity

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

No carcinogenicity long-term study is available for DIDP but an increase in incidence of hepatocellular tumours in rats related to peroxisome proliferation might be anticipated, in regard with the increased incidence in tumour liver cells observed with DEHP and DINP in carcinogenicity studies. Thus, there is no concern in regard with carcinogenicity

Summary on repeated-dose toxicity

The repeated-dose studies are summarised in the following table.

Species	Treat-ment	Substance Purity/dose	Body Weight	Clinical Signs	Biochemistry/ Haematology	Effects on organs		NOAEL	Reference
						Macroscopy	Microscopy		
Young Rat Fisher 344	21 days in diet	DIDP 99.84% pure 0-0.3-1.2-2.5%	↓ body weight 2.5%	No change	↓ serum triglycerides and cholesterol (1.2 and 2.5% males) ↑ cyanide – insensitive palmitoyl – CoA oxidation 1.2%-2.5% (female and male) ↑ 11 and 12 – hydroxylation of lauric acid 0.3-1.2-2.5% (males) ↑ 12 hydroxylation of lauric acid 2.5% (females)	↑ liver weight from 0.3% (males) from 1.2% (females) Kidney weight ↓ 2.5% Slight ↓ absolute testicular weight 2.5%	↓ hepatocyte cytoplasmic basophilia 1.2 and 2.5% ↑ eosinophilia (2.5%) No testicular change	0.3% (304 mg/kg/d for males) (264 mg/kg/d for females)	BIBRA (1986)
Rat Fisher 344	28 days in diet	0.020-0.05-0.1-0.3-1%	No change	-	↑ cyanide insensitive palmitoyl CoA oxidation from 0.1%	No testicular atrophy	No testicular atrophy	0.05% (57 mg/kg/d)	Lake et al. (1991)
Rat Sprague Dawley	28 days in diet	Palatinol Z 5,000 and 10,000 ppm	Slight ↓ in males	No change	No change	↑ liver weight 5,000 and 10,000 ppm	No change	5,000 ppm (600 mg/kg/d for males) (1,100 mg/kg/d for females)	BASF (1969a)
Rat Sprague Dawley	90 days in diet	Palatinol Z 800-1,600-3,200 & 6,400 ppm	Slight ↓ in male	No change	No change	↑ liver weight (absolute) at 6,400 ppm in males dose-related increase of liver weight from 1,600 ppm in females	No change No change	3,200 ppm (200 mg/kg/d for males) 800 ppm (60 mg/kg/d for females)	BASF (1969b)
Rat	90 days in diet	DIDP-FDA Grade 0.05-0.3-1%	Slight ↓ all doses in males 1% in females	No change	No change	↑ Liver weight 1%	No change	0.3% (200 mg/kg/d)	Hazleton (1968)
Dog (Beagles)	90 days in diet	0.05 - 0.3 - 1%	Slight ↓ 1%	No change	No change	↑ Liver weight 0.3-1%	swollen and vacuolated hepatocytes from 0.3%	0.05% (15 mg/kg/d)	Hazleton (1968)

Summary on toxicity on reproduction and fertility

In 42-44 day year old (pubertal) or adult rats there is no indication of organ reproductive effects evidenced by histological observation in repeated dose toxicity studies and the two-generation study. In the two-generation study decrease in mean percent normal sperm was observed but of low incidence and only in P1 generation. In pups (F1, F2 and in the cross fostering satellite group) decrease in testes weight and cryptorchidism in F2 high-dose offspring were observed likely due to the low body weight since no histopathological damages were observed in adult testes. There were no changes in Reproductive Indices. From those assays no adverse effects on fertility may be anticipated.
In regard with reproductive toxicity DIDP is a developmental toxicant since decrease in survival indices was observed consistently in both two-generation studies (Exxon Biomedical Sciences, 1997b; 2000) leading to the NOAEL of 0.06% (Exxon Biomedical Sciences, 2000). The NOAEL of 0.06% (33 mg/kg bw/day DIDP) is taken into account in the risk characterisation. In regard with developmental effects, skeletal variations are observed in the developmental studies at 1,000 mg/kg bw/day concurrently with slight signs of maternal toxicity and lead to a NOAEL of 500 mg/kg bw/day. In the two-generation rat study (Exxon Biomedical Sciences, 1997b) body weight decrease was observed in offspring partly related to lactation at the highest dose of 0.8% and leads to a NOAEL of 0.4% (253 to 761 mg/kg bw/day seeing that received doses are widely dependent on the period considered). Those NOAELs are considered for risk characterisation. No effects were seen on fertility thus no classification according to the EU is needed. With regard to development decrease in survival indices mainly in F2 (day 1 and day 4) in the two-generation study as well as skeletal variations in developmental studies are not severe enough to justify a classification.

ANNEX 2

Extract from CSTEE opinion on the results of the Risk Assessment of DIDP

Opinion expressed at the 24th CSTEE plenary meeting, 12 june 2001.

Repeated dose toxicity

DIDP has been studied for repeated dose toxicity mainly in rats, but results from studies using other species such as rabbit, cat and dog have also been reported. The route of administration is primarily by ingestion. Only one inhalation study was located. In this 14-day study in rats at 0.5 mg/l (aerosol) only a local irritant effect, but no systemic toxicity was found. The RAR assumes a NOAEL (systemic toxicity) of 0.5 mg/l. No studies using dermal exposure were located.

The liver was identified as the target organ following oral administration of DIDP in the feed for 28 or 90 days in rats. The liver effects found are consistent with peroxisome proliferation. In one of the 28-day repeated dose study reported (BASF 1969a) in the RAR a NOAEL of 600 mg/kg bw/day is given. However, in the NTP-CERHR of 2000 it is reported that all doses tested resulted in an increased absolute and relative liver weight. Thus, it seems that a NOAEL of 600 mg/kg bw/day may not be correct. In a 21-day feeding study in rats a NOAEL for increase in absolute liver weights in females was identified to be 264 mg/kg bw/day. In a second 28-day study a NOAEL for increased absolute liver weight was 57 mg/kg bw/day in male rats. Thus, it appears that female rats are somewhat more susceptible to DIDP-induced liver toxicity than males. Two 90-day studies are reported in the RAR. In the first of these studies (BASF, 1969b) a NOAEL for increased absolute liver weight of 200 mg/kg bw/day is assumed for male rats and 60 mg/kg bw/day for female rats based on relative liver weights. It is not clear why in male rats the NOAEL is based on absolute liver weight and in females on relative liver weight, especially since relative liver weights were increased at all dose levels tested in male rats. If relative liver weights are used also in males a LOAEL of 55 mg/kg bw/day is derived. In the second 90-day study (Hazelton Laboratories, 1968a) a NOAEL of 200 mg/kg bw/day is assumed based on increased liver weight and a minimal increase in thyroid activity. In addition to the rat studies one study in dogs has been reported. A dose-dependent increase in absolute liver weight was found, but the small number of animals used precluded statistical analysis. The RAR has assumed a NOAEL of 15 mg/kg bw/day whereas the NTP-CERHR Expert Panel has concluded that is not possible to derive a NOAEL for this study. Thus, a LOAEL of 77 mg/kg bw/day and 88 mg/kg bw/day for male and female dogs, respectively, should be considered. No relevant human data are available.

Mutagenicity

DIDP has been tested for mutagenicity *in vitro* and *in vivo*. No mutagenicity was found in bacterial tests or in mammalian cells (mouse lymphoma test). In the mouse lymphoma study DIDP was incompletely soluble and formed oily droplets at all concentrations tested. However, cytotoxicity was noted indicating that a sufficiently high concentration of DIDP was achieved. In the mice bone marrow micronucleus test DIDP was administered by gavage and not ip, which is the preferred route of administration to detect cytogenetic effects. DIDP was negative. The CSTEE agrees with the conclusion that the limited data available indicate that DIDP is non-genotoxic.

Carcinogenicity

DIDP has not been tested for carcinogenicity in experimental animals nor are there any available human data. Being a peroxisome proliferator one would suspect it to cause liver tumours in rat and/or mice carcinogenicity studies, as observed with other phthalates (DEHP and DINP). Both positive and negative cell transformation assays have been reported. The fact that DIDP does not interact with DNA and that peroxisome proliferation is generally accepted not to be associated with liver cancer in humans, leads to the conclusion that DIDP does not cause a concern for human cancer.

Reproductive toxicity

With respect to developmental toxicity two studies in rats and one in mice were found. No adverse effects on dams or offspring were noted when mice were administered a high dose of DIDP on gestation days 6-13. In the first rat study (Waterman et al., 1999) rats were administered DIDP by gavage on gestation days 6-15 at 0, 100, 500, or 1000 mg/kg bw/day. The CSTEE agrees with a NOAEL of 500 mg/kg bw/day for the dams. Waterman assumed a NOAEL for developmental effects of 500 mg/kg (based on skeletal variations on a per litter base). The NTP-CERHR Expert Panel Report (2000) disagreed with a developmental NOAEL of 500 mg/kg bw/day and a statistical re-evaluation of the data showed that a NOAEL of 100 mg/kg bw/day was more appropriate based on the incidence of cervical and accessory 14^{th} ribs. The re-analysed data shows a statistical increase at 500 mg/kg bw/day of skeletal variation, rudimentary lumbar ribs and supernumerary cervical ribs. Based on these data the CSTEE supports a NOAEL of 100 mg/kg bw/day for development. In the second rat study (Hellwig et al., 1997), rats (7-10 per dose group) were administered DIDP by gavage at 0, 40, 200, and 1000 mg/kg bw/day on gestation days 6-15. In this study a NOAEL of 200 mg/kg bw/day for maternal toxicity was derived and a NOAEL of 200 mg/kg bw/day for developmental toxicity (based on significant skeletal variation in the foetus) is assumed in the RAR. The CERHR Expert Panel, however, based on an increased incidence of dilated renal pelvis and hydroureter leading to a statistically significant increase in the mean percent of foetuses affected per litter with variations at the 200 and 1000 mg/kg bw/day, concluded that a NOAEL of 40 mg/kg bw/day was relevant. Based on the fact that several studies indicate that the effects on renal pelvis may be transient and that no renal effects were noted in the two-generation study, the CSTEE agrees that a NOAEL of 200 mg/kg bw/day is indicated. Further, the CSTEE agrees that an overall evaluation of the two rat studies suggests a maternal NOAEL of 500 mg/kg bw/day. However, the CSTEE does not support a NOAEL of 500 mg/kg bw/day based on skeletal variation. Both rat studies indicate a NOAEL of 100-200 mg/kg bw/day, and applying a conservative approach a NOAEL of 100 mg/kg bw/day is proposed.

Reproductive toxic effects have also been observed in one- and two-generation studies in rats.

No NOAEL could be derived from the one-generation study. In the first two-generation study no NOAEL of 253 to 761 mg/kg bw/day is assumed for developmental effects by the RAR. However, when the same study is evaluated by CERHR it is concluded that no NOAEL could be derived and that a reproductive toxic LOAEL of 131-152 mg/kg bw/day and 162-379 mg/kg bw/day in F_0 and F_1 dams during gestation and lactation, respectively, was appropriate. In the follow up two-generation study using lower doses, CERHR state that a reproductive toxic NOAEL of 38-44 and 52-114 mg/kg bw/day during pregnancy and lactation was identified by the study authors. The RAR concludes that no reproductive toxic effects were found at any dose tested. However, a NOAEL of 33 mg/kg bw/day could be derived for offspring toxicity in the F_2 generation (lowest estimated dose for 0.06% DIDP in the diet). The results of the one- and two-generation studies show that DIDP does not affect fertility in rats.

As stated above and based on the results of the prenatal studies, the CSTEE supports a NOAEL of 500 mg/kg bw/day for maternal toxicity. However, the CSTEE does not agree with the RAR in using of 500 mg/kg bw/day as a NOAEL for developmental toxicity. The CSTEE prefers a NOAEL of 100 mg/kg based on the re-evaluation of study data. Based on the second two-generation study, where a decrease in survival indices in the F_2 generation was noted, the CSTEE supports a NOAEL of 33 mg/kg bw/day as suggested in the RAR. The acceptance of 33 m g/kg bw/d as a NOAEL is based on NOAELs of 38-44 during pregnancy and 52-114 mg/kg bw/day during lactation, with respect to pup survival and growth in the cross-fostering and switched-diet satellite studies. Also, the first two-generation study showed a decrease in the survival index. The CSTEE does not agree that a NOAEL of 253 to 761 mg/kg bw/day should be used for the body weight decrease and prefer 127-151 mg/kg bw/day for gestation and 166-377 mg/kg bw/gay for lactation, as concluded by CERHR for the first two-generation study. The CSTEE agrees that DIDP should be considered a developmental toxicant. The CSTEE also agrees that DIDP does not affect fertility at doses up to 928 mg/kg bw/day based on the two-generation study and on the repeated dose studies in rats at doses up to 2100 mg/kg bw.