Annex XV dossier

PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, vPvB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Proposal for identification of DEHP as an SVHC

Substance Name: Bis(2-ethylhexyl)phthalate

EC Number: 204-211-0

CAS Number: 117-81-7

- *It is proposed to identify the substance as a CMR according to Article 57 (a), (b) and/or (c).*

This Annex XV dossier mainly builds on the agreed European Union Risk Assessment Report (RAR) on DEHP performed under regulation EEC 793/93 and the corresponding European Union Risk Reduction Strategy (RRS). Information from those documents is used in this dossier without giving full references in the dossier. Thus, the reader is referred to the RAR and the RRS (the latter is attached to this dossier). New information and new studies not used in the RAR and RRS are given as full references in the dossier.

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PROPOSAL FOR IDENTIFICATION OF A SUBSTANCE AS A CMR CAT 1 OR 2, PBT, VPVB OR A SUBSTANCE OF AN EQUIVALENT LEVEL OF CONCERN

Substance Name: Bis(2-ethylhexyl)phthalate

EC Number: 204-211-0

CAS number: 117-81-7

- *It is proposed to identify the substance as a CMR according to Article 57 (a), (b) and/or (c).*

Summary of how the substance meets the CMR (Cat 1 or 2), PBT or vPvB criteria, or is considered to be a substance of an equivalent level of concern

The substance is classified as toxic to reproduction, Category 2; R60-61.

Index Number (Annex I of Directive 67/548/EEC): 607-317-00-9

Registration number(s) of the substance or of substances containing the substance:

Not yet registered.

JUSTIFICATION

1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Chemical Name: 1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester

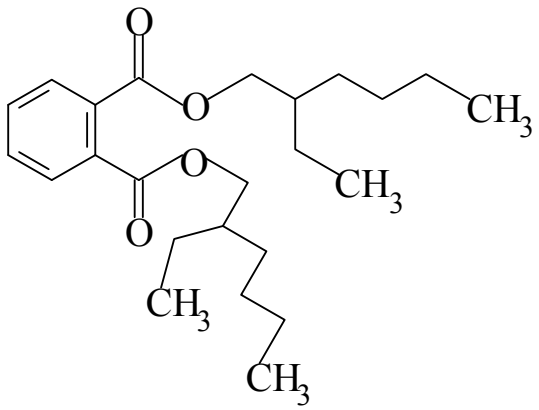
EC Name: Bis(2-ethylhexyl)phthalate

CAS Number: 117-81-7

IUPAC Name: Bis(2-ethylhexyl)phthalate

1.2 Composition of the substance

Data about purity indicate a high purity level (99.7 %). The impurities found are mainly other phthalates.

Chemical Name:	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester
EC Number:	204-211-0
CAS Number:	117-81-7
IUPAC Name:	Bis(2-ethylhexyl)phthalate
Molecular Formula:	$C_{24}H_{38}O_4$
Structural Formula:	
Molecular Weight:	390.6
Typical concentration (% w/w):	99.7
Concentration range (% w/w):	-

1.3 Physico-chemical properties

Table 1: Summary of physico- chemical properties

REACH ref Annex, §	Property	IUCLID section	Value
VII, 7.1	Physical state at 20°C and 101.3 kPa	3.1	Colourless oily liquid
VII, 7.2	Melting/freezing point	3.2	-55°C or -50°C
VII, 7.3	Boiling point	3.3	230°C at 5 mm Hg 385°C at 1013 hPa
VII, 7.5	Vapour pressure	3.6	0.000034 Pa at 20°C
VII, 7.7	Water solubility	3.8	3 µg/l at 20°C
VII, 7.8	Partition coefficient n-octanol/water (log value)	3.7 partition coefficient	7.5
XI, 7.16	Dissociation constant	3.21	-
	Henry's constant		4.43 Pa m^3/mol

2 MANUFACTURE AND USES

Not relevant for this type of dossier. However, see section about information on use, exposure, alternatives and risks.

3 CLASSIFICATION AND LABELLING

3.1 Classification in Annex I of Directive 67/548/EEC

Toxic to reproduction, Category 2; R60-61 (no specific concentration limits stated).

Index Number (Annex I of Directive 67/548/EEC): 607-317-00-9

3.2 Self classification(s)

Not relevant

4 ENVIRONMENTAL FATE PROPERTIES

4.1 Degradation

4.1.1 Stability

Photodegradation of DEHP (reaction with OH radicals) is important in the atmosphere ($T_{½}$ = 1 day), but the photolysis may become of less importance for DEHP bound to particles in the air. Photodegradation of DEHP is assumed to be of little importance in water and soil, and DEHP does not hydrolyse in water.

4.1.2 Biodegradation

4.1.2.1 Biodegradation estimation

Although some QSAR-models have indicated DEHP to be not readily biodegradable, the substance is classified as readily biodegradable based on actual studies (using adapted microorganisms) (see below).

4.1.2.2 Screening tests

The biodegradation of DEHP is varying in available studies. Based on the results of standard (aerobic) biodegradation test, DEHP is readily biodegradable, although it is failing the 10 day window.

4.1.2.3 Simulation tests

In eutrophic lake water 35–71% was mineralised at 29°C after 40 days. Based on this a half-life of 50 days, which is the value suggested by TGD for readily degradable substances failing the 10 day window, is chosen for the calculation of PEC for surface water in the EU RAR.

According to TGD, chemicals bound to solid phase are not degraded. Due to a high adsorption the EUSES model calculates a DT_{50} of 30,000 days in aerobic sediment. However, from available experimental data on degradation in sediment, an overall half-life of 3,000 days in sediment was estimated (300 days in the upper aerobic 10% of the sediment, no degradation in anaerobic sediment). These data are used in the calculation of PEC for sediment.

Anaerobic conditions and low temperature further reduce the degradation rate. Results from degradation studies of DEHP in agricultural soil are variable, but indicate moderate to low biodegradation rates. MEHP is the primary biodegradation product of DEHP.

4.1.3 Summary and discussion of persistence

DEHP can be regarded as abiotically rather stable, but biotic degradation does indeed occur, mainly under aerobic condition. Thus, DEHP can be classified as readily biodegradable, although the actual biodegradation rates in most media seem moderate. The estimated half-lives, based on available data for DHEP, are given in the Table 2 below.

Table 2: Selected biological degradation half-lives for DEHP used in the EU RAR

COMPARTMENT	DT_{50} (days)	BASED ON:
STP	0.029	TGD default *
Surface water	50	experimental data indicates that the default DT_{50} for readily biodegradable substances failing 10day window is more appropriate.
Agricultural soil	300	experimental data + temperature correction (Q10=2)
Aerobic sediment	300	experimental data
Anaerobic sediment	Infinite	default + experimental data
Sediment, overall	3,000	default (10 times of the half-life for aerobic sediment)

*Based on Classification: "Readily biodeg." (according to TGD)

4.2 Environmental distribution

4.2.1 Adsorption/desorption

With a log Kow of 7.5, DEHP is expected to be strongly adsorbed to organic matter. DEHP is therefore expected to be found in the solid organic phase in the environment. Hence, DEHP will be strongly adsorbed to the sludge in sewage treatment plants (unless the effluent is rich in dissolved organic matter which will increase the amount of DEHP in the water phase/effluent). The PCKOC model (Syracuse model, Meylan 1992) estimates Koc to 165,000 based on structure analysis, giving a log Koc for DEHP on 5.2 L/kg. DEHP is found to bioaccumulate in aquatic organisms, but DEHP does not bio-magnify. Due to its high affinity to organic matter only a limited bioaccumulation of DEHP in plants is expected.

4.2.2 Volatilisation

DEHP has a vapour pressure of $3.4 \cdot 10^{-5}$ Pa (at 20 to 25°C), which indicate a low evaporation rate from its pure state, and a Henry's law constant of 4.4 Pa m^3/mol, indicating a moderate evaporation from a pure water solution ('semi-volatile'). If released to the air, DEHP is likely to bind to particles.

4.2.3 Distribution modelling

Based on the above phys-chem parameters, a modelling using the Episuite level 3 fugacity model has been performed. It shows that of DEHP emitted into the environment, 87 % is expected to end up in soil, 10 % in sediment, 3 % in water, and only 0.1 % in air (a half-life of 300 days in sediment was assumed in the modelling). Monitoring data confirms that DEHP can be found in air and water, albeit, the majority of DEHP is found in sediment and soil.

4.3 Bioaccumulation

4.3.1 Aquatic bioaccumulation

4.3.1.1 Bioaccumulation estimation

There are measured data. See below.

4.3.1.2 Measured bioaccumulation data

The highest BCF values are observed for invertebrates, with 2,700 for Gammarus. In fish, the highest measured BCF_{fish} is 840 (fathead minnow). This indicates that uptake via the food chain might be an important exposure route, being of relevance for secondary poisoning. The BCFs, as well as monitoring data for different trophic levels, indicate that DEHP does not bio-magnify. This may in part be due to a more effective metabolisation rate in higher organisms.

4.3.2 Terrestrial bioaccumulation

Due to its high affinity to organic matter only a limited bioaccumulation of DEHP in plants is expected. The environmental studies confirm this with BCF ranging between 0.01 and 5.9. For earthworms a BCF of 1, based on experimental results and modelled data (EUSES), has been used in the EU risk assessment.

4.3.3 Summary and discussion of bioaccumulation

Measured bioconcentration factors show that DHEP can be accumulated in organisms at lower trophic levels, with BCFs of 2700 and 840 in invertebrates and fish, respectively. However, DEHP is not bio-magnified at higher trophic levels.

4.4 Secondary poisoning

Due to accumulation of DEHP in organisms at lower trophic levels (such as invertebrates (BCF≤2700) and fish (BCF≤840)), birds, mammals and fish feeding on invertebrates and fish will be exposed to DEHP. Thus, there is a potential for secondary poisoning, e.g., for birds eating mussels or worms, for mammals eating worms or fish, and for fish eating invertebrates.

The EU RAR has in some generic local scenarios indicated concern for mammals eating worms, and for birds eating mussels.

5 HUMAN HEALTH HAZARD ASSESSMENT

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

Generally, DEHP is rapidly absorbed from the gastrointestinal tract following oral administration. The extent of absorption in rats is around 50% for doses up to about 200 mg/kg bw. At higher doses, it appears that absorption in non-human primates is dose-limited in contrast to rodents. For humans, information is not, however, available concerning the dependency of oral uptake on dose. Also, the extent of oral absorption at doses which humans are expected to be exposed is not known. Absorption may be 100% at daily exposure levels. Limited data on toxicokinetics, following inhalation or dermal exposure, indicate that DEHP can be absorbed through the lungs whereas absorption through the skin appears to be limited. Following intra peritoneal injection most of the administered dose remains in the peritoneal cavity.

Distribution studies in rat indicate that DEHP is widely distributed in the body without evidence of accumulation in the tissues in rats. A comparative study of rats and marmosets showed similar distribution patterns in the two species (oral administration) whereas rats had higher tissue levels than marmosets. Thus, the difference in distribution between species is quantitative rather than qualitative.

The metabolism of DEHP involves several pathways and yields a variety of metabolites. The major step in the metabolism of DEHP is hydrolysis by lipases to MEHP (mono(2-ethylhexyl)phthalate) and 2-ethylhexanol, which is common to all investigated species.

MEHP is a relatively major component in urine of monkeys, guinea pigs and mice but was in most cases not detected in rat urine. However, MEHP is present in plasma in all species tested. The substance is excreted via the urine, mainly as MEHP-metabolites, but some excretion via bile also occurs in rodents. The elimination of DEHP largely depends on its metabolism and it might take 5-7 days to eliminate 80% of the DEHP administrated. The half-life for DEHP and its metabolites was 3-5 days in the adipose tissue and 1-2 days in the liver. The elimination is most rapid in rats.

In the DEHP data base, it has been observed that the oral absorption of DEHP to some extent is age-dependent, and the EU RAR is concluding on oral absorption percentages of 100 % in young animals and 50 % in adult animals.

DEHP can cross the placenta barrier and distribute into foetal tissues. In addition, DEHP can be transferred through the milk from lactating rats to their pups. Since the immature liver may have a lower metabolising capacity than that of older children and adults, infants and foetuses might be especially vulnerable to exposure to DEHP and MEHP.

5.2 Acute toxicity

5.2.1 Acute toxicity: oral

The acute oral toxicity of DEHP has been studied in several experiments of good quality. The LD_{50}-value in rats is > 20,000 mg/kg bw and in mice > 10,000 mg/kg bw. Only one report on the acute oral toxicity in humans has been located; the ingestion of 5 g caused no adverse effects, while 10 g caused mild gastric disturbances and “moderate catharsis”.

5.2.2 Acute toxicity: inhalation

In a study performed according to GLP principles, the toxicity of a single dose of DEHP via inhalation to rats was in excess of 10.6 mg/litre/4 hours.

5.2.3 Acute toxicity: dermal

The acute dermal toxicity of DEHP has not been investigated in any study of good quality. However, due to poor dermal absorption of DEHP, the acute dermal toxicity is expected to be low.

5.2.4 Acute toxicity: other routes

Following a single iv administration of DEHP in rats, effects were observed on the lungs including edema of the alveolar wall together with infiltration by leukocytes, hemorrage, and lethality (LD_{50}: 200 mg DEHP /kg).

5.2.5 Summary and discussion of acute toxicity

The data available on acute toxicity show a low acute toxicity and do not suggest a classification of DEHP according to EU criteria.

5.3 Irritation

Not relevant for this type of dossier.

5.4 Corrosivity

Not relevant for this type of dossier.

5.5 Sensitisation

Not relevant for this type of dossier.

5.6 Repeated dose toxicity

5.6.1 Repeated dose toxicity: oral

Numerous studies have investigated the toxicity of DEHP following repeated oral administration to experimental animals, preferably rats. Many of these studies are comparable to guideline studies and conducted in conformity with GLP. Critical organs for DEHP induced toxicity in laboratory animals are the testis, kidney, and liver.

In repeated dose studies, the lowest reported NOAEL for testicular effects, identified in a guideline study, is 50 ppm DEHP in the diet (3.7 mg/kg bw/day for 13 weeks), based on a high incidence of dose-related Sertoli cell vacuolation from the next higher dose level. However, because of some uncertainties caused by a rather high incidence of vacuolisation also in control rats, this NOAEL is not used. Instead, data from a three-generation study in rats, which showed an increased incidence of small testis suggest a NOAEL of 4.8 mg/kg/day, which is used for repeated dose effects on the testis.

The effects on the kidneys include: reduced creatinine clearance, increased absolute and relative kidney weights, increased incidence and severity of mineralization of the renal papilla, increased incidence and/or severity of tubule cell pigment, and increased incidence and/or severity of chronic progressive nephropathy. The majority of these changes were observed in both sexes, in different species following different exposure time. In long-term studies in rats and mice, there was no indication that DEHP-related changes in the kidney were reversible upon cessation of DEHP-exposure. On account of the DEHP-induced kidney toxicity observed in a well-performed 104-week-study in rats, a NOAEL of 28.9 mg/kg/day is suggested for kidney toxicity. The NOAEL is based on increased absolute and relative kidney weight in both sexes at the next higher dose level (LOAEL: 146.6 mg/kg bw/day in the males and 181.7 mg/kg bw/day in the females). A subsequent three-generation study in rats has indicated a LOAEL of 46 mg/kg/day for kidney weight increases, and a NOAEL of 14 mg/kg/day.

In the liver, the most striking effects observed are hepatomegaly due to hepatocyte proliferation (characterised by increased replicative DNA synthesis/cell division and hypertrophy), peroxisome proliferation, and hepatocellular tumours. A Working Group of the "International Agency for Research on Cancer" (IARC) have concluded that the mechanism by which DEHP increases the incidence of liver tumours in rodents (activation of PPAR-α and peroxisome proliferation) is not relevant to humans.

5.6.2 Repeated dose toxicity: inhalation

In experimental animals three inhalation studies are available. However, these studies are considered inadequate for risk assessment. In humans, there is a study suggesting that toxic damage of the lungs in preterm infants artificially ventilated with PVC respiratory tubes may be causally related to inhalation of DEHP. The estimated inhalative exposure ranged between 1μg/h – 4,200 μg/h DEHP.

5.6.3 Repeated dose toxicity: dermal

The only study available following dermal exposure to DEHP is inadequate for risk assessment.

5.6.4 Other relevant information

5.6.5 Summary and discussion of repeated dose toxicity:

The data available on repeated dose toxicity (not including reproductive effects) do not suggest a classification of DEHP according to EU criteria. In the risk characterisation for repeated dose toxicity, NOAELs for both testis and kidney toxicity are used. The NOAELs are 4.8 and 28.9 mg/kg/day, respectively.

5.7 Mutagenicity

The possible genotoxic effect of DEHP has been thoroughly investigated in several different short-term tests. The major metabolites of DEHP, MEHP and 2-EH, have also been examined. Most of the studies are performed according to GLP principles and are comparable to guideline studies.

The results have been negative in the majority of the *in vitro* and in *vivo* studies on DEHP, MEHP and 2-EH for detection of gene mutation, DNA damage, and chromosomal effects. The more conclusive positive results were obtained on cell transformation, induction of aneuploidy and cell

proliferation. These test systems are, however, also sensitive to several non-genotoxic substances such as tumour promoters and/or peroxisome proliferators. Taking all negative and positive results together, DEHP and its major metabolites are considered to be non-mutagenic substances in humans.

5.7.1 In vitro data

See above.

5.7.2 In vivo data

See above.

5.7.3 Human data

See above.

5.7.4 Other relevant information

See above.

5.7.5 Summary and discussion of mutagenicity

The data available on genotoxicity do not suggest a classification of DEHP according to the criteria for classification and labelling of dangerous substances (Annex IV to Commission Directive 93/21/EEC of 27 April 1993 adapting to technical progress for the 18th time Council Directive 67/548/EEC).

5.8 Carcinogenicity

5.8.1 Carcinogenicity: oral

The carcinogenicity of DEHP has been investigated in numerous animal studies. Four long-term studies performed in rats and mice are of good quality and are considered adequate for evaluation of carcinogenicity of DEHP in experimental animals. DEHP shows clear evidence of hepatocarcinogenicity in both sexes of rats and mice in the four different studies. The increase in tumour incidence in the liver was statistically significant and a dose-response relationship exists. In rats, an increase in the incidence of mononuclear cell leukaemia (MCL) was also observed, significant in males of one study only. In rats, the LOAEL and the NOAEL for tumour induction (both liver tumours and MCL) were established as 2,500 ppm (147 mg/kg bw/day for males) and 500 ppm (29 mg/kg bw/day for males) DEHP in the diet, respectively. In mice the LOAEL and the NOAEL for induction of liver tumour is 1,500 ppm (292 mg/kg bw/day for males) and 500 ppm (98 mg/kg bw/day for males) DEHP in the diet, respectively. Additionally, an increase in the incidence of Leydig cell tumours in male rats exposed for DEHP has been reported.

A feasible mechanistic basis for hepatocarcinogenicity through activation of peroxisome proliferator activated receptor alpha (PPARα) has been accepted by most of the experts in this field. However, there is still no clear evidence showing that the carcinogenicity of DEHP in rodents is mediated through activation of PPARα. It has been suggested that the hepatocarcinogenic effects of peroxisome proliferators, such as DEHP, in experimental animals are rodent-specific and irrelevant

for humans. This position is held by a number of experts and is a defensible conclusion based on the available mechanistic data. Notwithstanding, there are also arguments still indicating that a certain human cancer risk cannot, with certainity, be excluded. However, a Working Group of the "International Agency for Research on Cancer" (IARC) has concluded that the mechanism by which DEHP increases the incidence of liver tumours in rodents (activation of PPAR-α) is not relevant to humans.

Male rats exposed to DEHP showed an increase in the incidence in Leydig cell (LC) tumours. The relevance for humans of rodent LC tumours has been evaluated in an international workshop as well as in a published review. It was concluded that the pathways for regulation of the Hypothalamo-Pituitary-Testis (HPT)-axis in rats and humans are similar and hence, compounds that induce LCTs in rats by disruption of the HPT-axis pose a risk to human health with exception of two classes of compounds GnRH and dopamine agonists. Since it has been demonstrated that DEHP and other phthalates has a direct effect on the foetal testes the two latter mechanisms are not relevant for phthalates, and the induction of LC tumours in rats exposed for pthalates should be regarded as relevant to humans taking into consideration the species differences in sensitivity. In conclusion, the presented evidence for the phthalates-induced LC tumours in rats, and the possible endocrine effects of phthalates, together with the fact that developing rats are more sensitive to the phthalates-induced testicular toxicity than sexually mature animals, should be considered seriously. Especially, when related to the limited human data suggesting an increased risk for testicular cancer in workers in PVC-industry. However, a careful evaluation of the available data is necessary before concluding on the possible carcinogenic risk of DEHP.

An increase in the incidence in mononuclear cell leukemia (MCL) was observed in male rats exposed to DEHP. Whereas some experts consider MCL in F344 rats as having similar pathology to an uncommon human tumour (large granular lymphocytic leukemia) and representing a unique model for study of natural tumour immunity, other experts regard MCL as F344 rats-specific, with little relevance for humans. Based on the available data the relevance for humans of the DEHP-induced MCL in F344 rats is not clear.

5.8.2 Carcinogenicity: inhalation

In experimental animals, the only inhalation study available is on hamsters, and is considered inadequate for risk assessment as only one dose of DEHP was used in the study. Also, the dose of DEHP used was very low and the maximal tolerated dose (MTD) was not reached as no signs of any toxicological effects were reported.

5.8.3 Carcinogenicity: dermal

No data available.

5.8.4 Carcinogenicity: human data

No relevant study in humans on the carcinogenicity of DEHP is available.

5.8.5 Other relevant information

5.8.6 Summary and discussion of carcinogenicity

Based on the overall evaluation of the available data, no classification for carcinogenicity is proposed.

5.9 Toxicity for reproduction

The most important studies are briefly described below in Table 3 and Table 4 (section 5.9.1 and 5.9.2). An overall discussion of the data follows in section 5.9.5.

5.9.1 Effects on fertility

Table 3: Summary of important reproductive studies with DEHP in laboratory animals

Species	Protocol	Results	References
Repeated dose (testicular) toxicity studies			
Rat, F344 10 rats/sex/group	13 weeks, via the *diet* 0, 1,600, 3,100, 6,300, 12,500 or 25,000 ppm (0, 80, 160, 320, 630, or 1,250 mg/kg/day)	↓bw gain at 25,000 ppm testis atrophy from 12,500 ppm NOAEL 6,300 ppm (320 mg/kg/day)	NTP (1982); see RAR
Rat, F344 50 rats/sex/group	103 weeks, via the *diet* 0, 6,000, or 12,000 ppm (0, 322, or 674 mg/kg/day [males])	↓bw at 12,000 ppm anterior pituitary: hypertrophy at 12,000 ppm (22/49 males, 45%) testis: seminiferous tubular degeneration at 6,000 ppm (2/44, 5%) and 12,000 ppm (43/48 males, 90%), histologically devoid of germinal epithelium and spermatocytes	NTP (1982); see RAR
Rat, Wistar 6 males (25-day-old) per dose group	0, 50, 100, 250, or 500 mg/kg bw for 30 days	Dose-dependent and significant ↑ LDH and GGT and ↓ SDH from 50 mg/kg bw; ↑ β-glucuronidase and ↓ acid phosphatase testis: marked destructive changes in the advanced germ cell layers and vacuolar	Parmar *et al.* (1995); see RAR

		degeneration at 250 and 500 mg/kg	
Rat, F344 70-85/sex/group recovery group: 55/sex	104 weeks, *diet* 0, 100, 500, 2500, or 12,500 ppm (0, 5.8, 28.9, 146.6, or 789.0 mg/kg bw/day [males]; 0, 7.3, 36.1, 181.7, or 938.5 mg/kg bw/day [females] or 12,500 ppm for 78 weeks, followed by a recovery period of 26 weeks	Pituitary: ↑ castration cells (30/60 males) at 12,500 ppm; Testis: ↓ weight, ↑ incidence and severity of bilateral hypospermia at 12500 ppm; Epididymis: ↑ immature or abnormal sperm forms and hypospermia from 12,500 ppm; Changes in the testis and pituitary were not reversible upon cessation of exposure NOAEL for testicular effects 500 ppm (28.9 mg/kg bw/day)	Moore (1996); see RAR
Rat, Sprague-Dawley 10 rats/sex/group	13 weeks, *diet* 0, 5, 50, 500, or 5,000 ppm (0, 0.4, 3.7, 37.6, or 375.2 mg/kg bw/day [males])	Testis: mild Sertoli cell vacuolation at 500 ppm (7/10); decreased absolute and relative testicular weight, mild to moderate Sertoli cell vacuolation, testicular atrophy and complete loss of spermatogenesis at 5,000 ppm (9/10), increased liver and kidney weights (all rats of both sexes), and mild histological changes of the thyroid at 5,000 ppm NOAEL 50 ppm (3.7 mg/kg bw/day)	Poon *et al*. (1997); see RAR
Mouse, B6C3F1 70-85/sex/group; recovery group: 55/sex	104 weeks, *diet* 0, 100, 500, 1,500 or 6,000 ppm (0, 19.2, 98.5, 292.2 or 1,266.1 mg/kg bw/day [males] or 6,000 ppm followed by a recovery	Testis: from 1,500 ppm ↓ weight, ↑ incidence and severity of bilateral hypospermia; Epididymis: from 1,500 ppm ↑ immature or abnormal sperm forms	Moore (1997); see RAR

	period of 26 weeks	and hypospermia; changes in testes partially reversible; NOAEL 500 ppm (98.5 mg/kg bw/day)	
Continuous breeding studies			
Mouse, ICR 20 animals/sex/dose group, 40 control animals of each sex	*Diet*, 98 days 0, 0.01, 0.1, or 0.3% (0, 20, 200 or 600 mg/kg bw/day)	Dose-dependent ↓ in the number of litters and proportion of pups born alive from 0.1% (0.1%: 14/19 fertile, 0.3%: 0/18); ↑ absolute and relative liver weight (both sexes) and ↓ reproductive organ weights and atrophy of seminiferous tubules at 0.3%; no effect on bw NOAEL for maternal and developmental toxicity 20 and 600 mg/kg bw/day, respectively <u>crossover mating trial:</u> treated males and control females: 4/20 fertile; control males and treated females: 0/16 fertile	Lamb *et al*. (1987); see RAR
See also the **multi-generation studies** described below in section 5.9.2			

5.9.2 Developmental toxicity

Table 4: Summary of important developmental toxicity studies in laboratory animals

Developmental toxicity Studies			
Rat, F344/CrlBr 34-25 females/group	*Diet* 0, 0.5, 1.0, 1.5, or 2% gestation days 0-20	↓ maternal food intake and mean foetal bw from 0.5%; ↓ maternal bw gain, ↑ absolute and relative liver weights, ↓ foetal bw/litter from 1.0% ↑ number and percentage of	NTIS (1984); Tyl *et al*. (1988); see RAR

		resorptions, non-live and affected implants/litter at 2%; NOAEL for maternal and developmental toxicity 0.5% (~357 mg/kg bw/day)	
Rat, Wistar 9-10 females/group	*Gavage*, oil 0, 40, 200 or 1,000 mg/kg bw/day on gestation days 6-15	↓ maternal bw and ↑ maternal relative kidney and liver weights at 1,000 mg/kg bw ↓ number of live foetuses/dam ↓ foetal body weights, ↑ number of malformed foetuses/dam (tail, brain, urinary tract, gonads, vertebral column, and sternum) at 1,000 mg/kg bw; NOAEL for maternal and developmental toxicity 200 mg/kg/day	BASF (1995); Hellwig *et al*. (1997); see RAR
Mouse, 1-CR 30-31 females/group	*Diet*; 0, 0.025, 0.05, 0.10 or 0.15% (0, 44, 91, 190.6 or 292.5 mg/kg bw/day); gestation days 0-17	↓ maternal body weight gain from 0.10% (mainly due to ↓ uterine weight, ↓ foetal body weight and number of live foetuses per litter); ↑ number and percent of resorptions, late foetal deaths, dead and malformed foetuses, and percent malformed foetuses/litter from 0.05% (open eyes, exophtalmia, exencephaly, short, constricted or no tail); visceral malformations and skeletal defects (fused and branched ribs, misalignment, and fused thoracic vertebral centra); NOAEL for maternal toxicity 0.05% (91 mg/kg bw/day) and	NTIS (1984); Tyl *et al*. (1988); see RAR

		for develop-mental toxicity 0.025% (44 mg/kg bw/day)	
Mouse, CD-1 15 females/dose group30 controls	*Oral*, gavage 0, 40, 200 or 1,000 mg/kg bw/day gestation days 6-15	Foetotoxic effects at 200 mg/kg bw/day ↓ number of viable foetuses ↑ number of resorptions and post-implantation losses at 1,000 mg/kg bw/day and also cardiovascular abnormalities, tri-lobed left lungs, fused ribs, fused thoracic vertebral centres and arches, immature livers, and kidney abnormalities NOAEL 200 mg/kg bw for maternal toxicity and NOAEL 40 mg/kg bw/day for developmental toxicity	Huntingdon (1997); see RAR
Two-generation studies			
Rat, Sprague-Dawley 17/males/group	3 generations via *diet*; 1.5, 100, 300, 1,000, 7,500 and 10,000 ppm (0.1, 0.5, 1.4, 4.8, 14, 46, 359, and 775 mg/kg/day	Dose-dependent effects on numerous testis-related parameters. NOAEL for testicular toxicity and developmental toxicity and 46 mg/kg/day for fertility	Wolfe *et al. (*2003); see RAR
Rat, Wistar, 25 animals/group	0, 1,000, 3,000 or 9,000 ppm DEHP via the *diet* (corresponding to approximately 0, 113, 340 or 1,088 mg/kg/day)	3,000 ppm: reduced testis weight in F2, focal tubular atrophy and a feminisation of 49% of the male offspring. Minimal focal tubular atrophy also occurred at 1,000 ppm (113 mg/kg and day), which thus constitutes a conservatively chosen LOAEL	Schilling *et al.* (2001); see RAR
Muse, CD-1 (number not	*Diet*, 0.01, 0.025, or 0.05%	↑ prenatal mortality for F1-litters at 0.05%	NTIS (1988); see RAR

specified)	(0, 19, 48 or 95 mg/kg bw/day)	↓ number of viable pups neonatally at 0.05% NOAEL for parental toxicity and F2-offspring: 0.05% (95 mg/kg bw/day) NOAEL for F1-offspring: 0.025% (48 mg/kg bw/d)	
Post-natal studies			
Rat, Sprague-Dawley 10 males/group	*Gavage*, corn oil 5 days from the age of 1 week, 2 weeks, 3 weeks, 6 weeks, or 12 weeks 0, 10, 100, 1,000 or 2,000 mg/kg bw/day	Two doses of 2,000 mg/kg bw were fatal for most pups in the three youngest age groups, ↓ bw for 6- and 12-week-old rats but no mortalities; 5 doses of 1,000 mg/kg bw: ↓ bw gain in 1-, 2-, and 3-week-old rats; ↑ absolute and relative liver weights at 100 mg/kg bw/day in all age groups (except for 1-week-old rats) and in all age groups at higher dose levels; ↓ plasma cholesterol levels in weanling and adult rats from 1,000 mg/kg/day	Dostal *et al*. (1987b); see RAR

5.9.3 Human data

No human data on the effect of DEHP on fertility is available.

5.9.4 Other relevant information

Studies performed after the EU RAR on DEHP was agreed have not been thoroughly evaluated. However, there are recent studies that may seem to support a NOAEL for testicular toxicity of the magnitude agreed in the RAR (e.g., Andrade *et al*., 2006a, 2006b, 2006c).

Several phthalates seem to have similar toxicological profiles with respect to testicular effects, and there are good indications that DEHP, dibutylphthalate (DBP) and diisobutylphthalate (DiBP) may have similar mechanisms of action (Borch *et al*., 2006a, 2006b). The risks from the combined exposure to several different phthalates thus need to be considered.

5.9.5 Summary and discussion of reproductive toxicity

Available data demonstrate that exposure to DEHP affects both fertility and reproduction in rodents of both sexes and also produces developmental effects in offspring. In males, DEHP induces severe testicular effects, including testicular atrophy. Testicular effects have been observed in numerous repeated dose toxicity studies in rats, mice and ferrets. In addition, minor effects were observed in hamster exposed to DEHP and more severe effects induced by MEHP. In the available studies marmosets were not sensitive to DEHP. No studies on testicular effects in rabbits are available. MEHP is believed to be the active metabolite of DEHP affecting testes and reproductive functions both *in vivo* and *in vitro*. The possible role of other metabolites is, however, not fully elucidated.

The NOAEL for testicular effects, as identified in a guideline three-generation reproductive toxicity study (Wolfe *et al*., 2003; see RAR), is 4.8 mg/kg/day. A NOAEL of 3.7 mg/kg bw in rats was indicated based on a high incidence (7/9) of Sertoli cell vacuolation at the next higher dose level (500 ppm equivalent to 37.6 mg/kg bw) in a 13-week guideline study (Poon *et al.*, 1997; see RAR). At the highest dose level (5,000 ppm, equivalent to 375.2 mg/kg body weight) also a high incidence of atrophy of the seminiferous tubules with complete loss of spermatogenesis was found in addition to a higher incidence of cytoplasmic Sertoli cell vacuolation (9/10). However, as there remains some doubts as to the toxicological significance of the Sertoli cell vacuolisation observed in the Poon study, a NOAEL of 4.8 mg/kg/day (100 ppm) is chosen from the Wolfe study (2003), based on occurrence of small male reproductive organs (testis/epididymes/seminal vesicles) and minimal testis atrophy (exceeding those of the current controls as well as historical control groups) at 300 ppm and above.

Both *in vivo* and *in vitro* experiments have demonstrated that the Sertoli cell is one of the main targets for DEHP/metabolite-induced testicular toxicity producing subsequent germ cell depletion (Poon *et al.*, 1997; Arcadi *et al*., 1998; Li *et al*., 1998; see RAR). Sertoli cells provide both physical support as well as secreting factors that are required for germ cell differentiation and survival and may also influence the signal transduction mechanism between these cells. Study results have also shown that DEHP and MEHP may exert a direct effect on Leydig cell structure and function as determined by testosterone output and also that DEHP and MEHP produce similar changes *in vivo* and *in vitro* in both Leydig cells and in Sertoli cells (Jones *et al*., 1993; see RAR). It is plausible that malfunction of Leydig cells affects the physiology of adjacent Sertoli cells. Findings also indicate that different phthalates may exert changes that are unique to one or common to both cell types.

Developing and pre-pubertal rats have been found to be much more sensitive to exposure to DEHP than adults (Gray and Butterworth, 1980; Sjöberg *et al*., 1985c; 1986b, Arcadi *et al*., 1998; Wolfe *et al*., 2003; see RAR). The younger animals respond to a much lower dose or produce a more serious lesion with a comparable dose on a mg/kg/day basis. In some instances, the onset for the production of the lesion is also more rapid. Exposure of rats prenatally and during lactation has produced irreversible effects at dose levels inducing only minimal effects in adult animals at the same exposure levels (Arcadi *et al*., 1998; Wolfe *et al*., 2003; see RAR).

Based on the available data, which varies in both the study designs and number of animals included**,** testicular effects have been demonstrated in both male rodents and non-rodents: rat (NOAEL = 4.8 mg/kg bw/day), mouse (NOAEL = 98.5 mg/kg bw/day), and ferret (LOAEL = 1,200 mg/kg/day) (Poon *et al*., 1997, Moore, 1997; Lake *et al*., 1976; see RAR). In addition, minor effects were observed in hamster exposed to DEHP and more severe effects were induced by MEHP (Gray *et al*., 1982; see RAR). In the available studies with marmosets, testicular toxicity has not been observed after treatment with DEHP (Kurata *et al*., 1995; 1996; 1998; see RAR). The reasons for the differences in study results have been suggested to be caused by toxicokinetic differences.

Moreover, other factors such as animal age, study design, animal model selection have also to be considered. For instance, marmosets which are new-world monkeys vary in their metabolic pathways and capacities and are not as closely related to humans as are cynomolgus and Rhesus monkeys (old-world monkeys) **(**Caldwell, 1979a; 1979b; see RAR). Although Sertoli cell replication seems to be more similar in man and marmosets, and the efficiency of spermatogenesis is poor in marmosets as well as in humans, there is, however, no evidence to support that the results obtained in pre-pubertal rats are not relevant for man or that use of adult marmosets should be preferred. Other mechanism(s) and/or factors that caused the observed differences in the DEHP-induced testicular toxicity have not, however, been fully substantiated. Based on the available animal data it is not possible to definitely conclude the relevance of these differences to humans. However, in the limited toxicokinetic data in humans, MEHP, the testicular toxicant, is formed following exposure to DEHP. Therefore, DEHP-induced testicular effects observed in animal studies are considered relevant for humans.

Effects on male fertility have been observed in mice and rats. In mice, DEHP adversely affects the number of fertile matings. In a continuous breeding study, an oral NOAEL of 0.01% in the diet (20 mg/kg bw/day) was identified for fertility (Lamb *et al*., 1987; see RAR). In rat, the oral NOAEL for body weight, testis, epididymis and prostate weights and for endocrine and gonadal effects in male rats was considered to be 69 mg DEHP/kg bw/day in a 60 day study (Agarwal *et al.*, 1986a; 1986b; see RAR). In a complementary crossover mating trial, females given 0.3% DEHP were more seriously affected than males. None of the females were able to produce pups: the fertility index was 0 (0/16) for females and 20% (4/20) for males compared to 90% for the control group (18/20).

Developmental toxicity has been observed in several studies. The rat has been shown to be the most sensitive species to DEHP-induced malformations. Irreversible testicular damage in the absence of obvious effects on the dams was shown in male pups exposed *in utero* and during lactation at very low dose levels (LOAEL = 3.5 mg/kg bw/day) (Arcadi *et al*., 1998; see RAR). Their mothers were exposed to DEHP in drinking water at doses from about 3 mg/kg/day during pregnancy and lactation. However, there is some uncertainty with regard to the actual concentration of DEHP in the water. Alterations in kidneys tended to ameliorate with time; the testicular lesions did, however, not appear to reduce with growth. Histopathological changes were still observed at termination of the study, 8 weeks after delivery. The same levels of exposure did not produce similar effects in adult male rats. Effects on the male reproductive system, partly induced during the gestational period, were also observed in a three-generation study with a NOAEL of 4.8 mg/kg/day (Wolfe *et al*., 2003; see RAR). In mice, DEHP is embryotoxic and teratogenic at oral dose levels below those producing observable evidence of toxicity to the dams.

In a continuous breeding study in mice, an oral NOAEL for maternal and developmental toxicity of 600 and 20 mg/kg bw/day were identified, respectively (Lamb *et al*., 1987; see RAR). In a developmental toxicity study an oral NOAEL of 44 mg/kg bw/day was identified. The NOAEL for maternal toxicity was 91 mg/kg bw/day (NTIS, 1984; Tyl *et al*., 1988; see RAR). In a dietary 2-generation study in mice, the maternal NOAEL was 0.05% DEHP (91 mg/kg bw/day) and the NOAEL for F1 offspring 0.025% (48 mg/kg bw/day) (NTIS 1988; see RAR).

A few developmental toxicity studies have been performed in other species. These studies are, however, inconclusive. Only one developmental study is available concerning the effects of exposure to DEHP by inhalation (Merkle *et al*., 1988; see RAR) However, this study is considered inconclusive and not useful for risk assessment. Because of uncertainties regarding the actual dosing in the study by Arcadi *et al*. (1998), which has given the lowest effect level, the NOAEL of 4.8 mg/kg/day (Wolfe *et al*., 2003; see RAR) is selected for developmental toxicity.

Animal data have shown that DEHP and its metabolites can be transferred to pups via mother's milk in concentrations sufficient to cause toxicity (Parmar *et al*., 1985, Dostal *et al*., 1987a, Tandon *et al*., 1990; see RAR).

Both *in vivo* and *in vitro* study results indicate that DEHP can interfere with the endocrine function and also influence the sexual differentiation (e.g. Gray *et al*., 1999 and Jones *et al*., 1993; see RAR). Due to the effects on the Leydig cells as measured by a decreased testosterone output, it cannot be excluded that DEHP may exert an antiandrogen effect. The results of recently performed *in vivo* studies in rats exposed to DEHP or DBP support the hypothesis that exposure to phthalates may be provoked by an antiandrogen mechanism (Gray *et al*., 1999, Mylchrest and Foster, 1998; see RAR). The present data in experimental animals are of concern for humans.

To summarize, based on a 3-generation study in rats, a NOAEL of 4.8 mg/kg/day is chosen for developmental toxicity and for repeated dose toxicity on the testis based on testicular toxicity in developing rats at a dose of 14 mg/kg/day (Wolfe *et al*., 2003; see RAR). For effects on fertility a NOAEL of 20 mg/kg/day was chosen from a continuous breeding study in mice, where fertility was affected at the next higher dose of 200 mg/kg/day (Lamb *et al*., 1987; see RAR).

5.10 Other effects

5.11 Derivation of DNEL(s) or other quantitative or qualitative measure for dose response

5.11.1 Overview of typical dose descriptors for all endpoints

In the animal toxicity studies, DEHP has been shown to cause toxic effects after repeated dose exposure, by affecting the reproductive outcome and the target organs testis and kidney. The key studies and the effects observed are described further in Table 5 below. The nature of the DEHP-induced toxic effects is considered serious, and could involve endocrine disruption. Effects on the testis, fertility, development, and kidney (repeated dose toxicity) are thus considered to be the most critical effects. Severe and irreversible testicular injury was induced in rats exposed to low oral dose levels of DEHP in three different studies (Wolfe et al., 2003; Poon et al., 1977; Arcadi et al., 1998; see RAR). Also severe developmental effects were observed in rats and mice in the absence of maternal toxicity (Wolfe et al., 2003; Arcadi et al., 1998; Lamb et al., 1987; see RAR). Thus, consideration is given to the fact that the endocrine effects (e.g. underlaying the testicular toxicity) are very serious effects, and that the sensitivity to this effect is highest during gestation and the first few months after birth when the most sensitive systems are still developing. In the EU RAR, a conservative oral NOAEL of 4.8 mg/kg/day was identified for testicular/developmental toxicity, and became the leading NOAEL in the risk characterisation. [1]

[1] A study published after the RAR was finalised seems to support a NOAEL of this magnitude (Andrade et al. 2006, A dose-response study following in utero and lactatinal exposure to di-(2-ethylhexyl)-phthalate (DEHP): Non-monotonic dose-response and low dose effects on rat brain aromatase activity. Toxicology 227, 185-192. Andrade et al. 2006, A dose-response study following in utero and lactatinal exposure to di-(2-ethylhexyl)-phthalate (DEHP) : Reproductive effects on adult male offspring rats. Toxicology 228, 85-97. Andrade et al. 2006, A dose-response study following in utero and lactatinal exposure to di-(2-ethylhexyl)-phthalate (DEHP) : Effects on androgenic status, developmental landmarks and testicular histology in male offspring rats. Toxicology 225, 64-74).

There is no concern for acute toxicity, irritation, sensitisation, mutagenicity, or carcinogenicity, and these end-points are therefore of no relevance for setting DNELs.

Table 5: Studies showing the critical endpoints and NOAELs for DEHP

Species	Study Protocol; Quality	Effects observed at LOAEL	LOAEL (mg/kg bw/day)	NOAEL (mg/kg bw/day)	Ref.
Repeated-dose toxicity					
Rat, F-344, males and females	Diet, 2 years; GLP, comparable to guideline study	Repeated dose toxicity, increased absolute and relative kidney weight in both sexes. More severe kidney lesions were observed at the highest dose level.	147	29	Moore (1996); see RAR
Reproductive toxicity					
Rat, Sprague-Dawley, males and females	Diet, 3-generation guideline study	Testicular toxicity (RdT) as well as Developmental toxicity: increased incidences of small testes, epididymes, and seminal vesicles, as well as cases of minimal testes atrophy. The toxicity was aggravated by exposure during the gestational/pup-period.	14	4.8	Wolfe et al. (2003); see RAR
Mouse, CD-1, males and females	Diet, continous breeding study; GLP, comparable to guideline study	Fertility was decreased (dose-dependent ↓ in the number of litters) and decreased proportion of live pups; crossover matings showed that both sexes were affected.	200	20	Lamb et al. (1987); see RAR

5.11.2 Correction of dose descriptors if needed (for example route-to-route extrapolation)

In the DEHP data base, it has been observed that the oral absorption of DEHP to some extent is age-dependent, and the EU RAR is concluding on oral absorption percentages of 100 % in young animals and 50 % in adult animals. The human oral absorption efficiency is not known, but 100 % oral absorption was concluded as a reasonable worst case estimate. Therefore, the dose descriptors obtained from studies on adult animals has to be corrected for the possible difference in absorption between adult animals and humans (50 % vs 100 %, respectively). This need for correction applies to two of the studies above (Moore et al 1996 and Lamb et al 1987; see RAR), since they are conducted on adult animals. The observed RdT NOAEL for kidney toxicity (29 mg/kg/day) obtained from a chronic study on adult rats is corrected into a systemic NOAEL of 14.5 mg/kg/day, whereas the observed fertility NOAEL (20 mg/kg/day) is corrected into a systemic NOAEL of 10 mg/kg/day. For the NOAELs coming from the 3-generation study (testicular toxicity and developmental toxicity), no recalculation to a systemic NOAEL is needed as a major part of the exposure occurs during life stages with an assumed oral absorption of 100%. The corrected 'systemic' NOAELs are given below in Table 6.

Table 6: Summary of corrected oral NOAELs used for the setting of DNELs

Effect	Route	LOAEL (mg/kg bw/d)	NOAEL (mg/kg bw/d)	$NOAEL_{systemic}$[1] (mg/kg bw/d)
RDT Kidney toxicity [2]	Oral	147	29	14.5
RDT Testicular toxicity [3]	Oral	14	4.8	4.8
Fertility [4]	Oral	200	20	10
Developmenta l[3]	Oral	14	4.8	4.8

1) Correction of NOAEL for 50% oral absorption in adult rats
2) 2-year oral study in rats (Moore 1996)
3) Three-generation oral study in rats (Wolfe et al., 2003). No correction of the NOAEL is needed as the study is considered to directly give a systemic NOAEL (mainly exposure of young animals with 100% absorption)
4) Continuous breeding study in mice (Lamb et al.,1987)

The oral NOAELs can be transformed using route to route extrapolation into NOAELs also for inhalation and dermal exposure, but that has not been done in the context of this Annex XV SVHC dossier.

5.11.3 Application of assessment factors

In the EU RAR on DEHP, total AFs of 100-250 have been used for the general population, with the higher values applying for new-born babies. The total factor was made up of an interspecies factor of 10, an intraspecies factor of 10, and an additional factor of 2-2.5 for babies in consideration of the severity of effect and the high sensitivity of new-born babies for the testicular toxicity. For workers, a total AF of about 30 was used.

However, the new DNEL guidance document is to some extent advocating the use of approaches not used in the EU RAR on DEHP, and the REACH-approach will therefore be followed below.

The assessment factors used have to cover uncertainties with regard to extrapolations between species, within humans, and if studies are shorter than the human exposure duration. AFs should also be used if there are issues relating to the dose-response, the severity of effects, and for the quality of the total database.

For interspecies extrapolation, a factor of 10 is used for the rat studies. This factor is made up of a factor of 4 for allometric scaling times a factor of 2.5 for remaining uncertainties regarding the sensitivity (too little is known about the mechanism of action to permit speculations on the sensitivity of humans vs rodents). For the mouse fertility study (Lamb et al 1987; see RAR), the factor becomes 17.5, as the allometric scaling factor between mice and humans is 7 (7 x 2.5=17.5). The intraspecies factor is 5 for workers and 10 for the general population. All studies cover chronic exposure, so there is no need for an AF for duration correction. There are no issues relating to the dose-response or for the quality of the total database. For the subpopulation of babies, the severity is an issue, which is further discussed below. The overall AFs are given in Table 7 below for the general population and workers. The table also gives the oral DNELs for the different endpoints (with 2 decimals).

Table 7: Derivation of oral DNELs for the different endpoints

Endpoint	Corrected oral dose descriptor[1] (mg/kg/day)	Overall AF applied		Endpoint specific oral DNEL	
		General population	Workers	General population (mg/kg/day)	Workers (mg/kg/day)
RDT testis	4.8	100	50	0.05	0.1
RDT kidney	14.5	100	50	0.14	0.29
Fertility	10	175	88	0.06	0.11
Dev tox	4.8	100	50	0.05	0.1

[1] No local effects are of relevance for DEHP.

In the EU RAR on DEHP, separate risk characterisations were performed for the subpopulation of babies, mainly because there are specific exposure of babies through, e.g., pacifiers and toys. However, it was also identified that the infant group is the most sensitive age group for the testicular toxicity of DEHP, that the effect is irreversible and thus of high severity. It was also acknowledged that there is additional exposure of infants to other phthalates that are toxic to reproduction via similar mechanisms of action as DEHP. As an illustration of potential for exposure, indoor dust in the UK contains dibutylphthalate (DBP, median 53 μg/g dust) and butylbenzylphthalate (median 24 μg/g dust) (Santillo et al., 2003; see RAR). Their monoester metabolites are also found in urine of American children (Brock et al., 2002; see RAR) and the presence of monobutylphthalate in breast milk has been indicated. Biomonitoring performed in Germany after the RAR was finalised indicates exposure of adult Germans to DEHP, DBP and BBP at roughly similar levels, both when measured as urinary metabolites (Wittasek et al 2007a) and in diet samples (Fromme et al 2007a). Similar, and possibly additive, effects of DEHP and DBP have been indicated, e.g., in a study by Borch et al 2006 (which was not reviewed in the EU RAR). However, the possible impact of co-exposure to other phthalates was not allowed to be assessed in the ESR risk assessment of DEHP, and an agreed methodology for doing that is also lacking. Overall, an additional AF of 2-2.5 for the severity of effect and the issues discussed above was used in the EU RAR, although all member states did not agree to this additional factor.

We propose using an additional AF of 2 for the reasons given above for setting a DNEL specific for infants. The resulting DNELs would become 0.02, 0.72, and 0.03 mg/kg/day for RDT testis, RDT kidney, and fertility, respectively (developmental toxicity is of no relevance for infants).

5.11.4 Selection/ identification of the critical DNEL(s)/ the leading health effect

In this Annex XV SVHC dossier, only oral DNELs have been set. Three different subpolulations have been assessed, and the critical DNELs (rounded to 2 decimals) are presented in **Fel! Hittar inte referenskälla.** below.

Table 8: Summary of the leading population-specific oral DNELs

Population	**End-point(s)**	**Oral DNEL**
Workers	Testicular / developmental toxicity	0.10 mg/kg/day
The general population	Testicular / developmental toxicity	0.05 mg/kg/day
Infants (males)	Testicular toxicity	0.02 mg/kg/day

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO-CHEMICAL PROPERTIES

Not relevant for this type of dossier.

7 ENVIRONMENTAL HAZARD ASSESSMENT

7.1 Aquatic compartment (including sediment)

7.1.1 Toxicity test results

7.1.1.1 Fish

Short-term toxicity to fish

Several reliable short-term studies on effects of DEHP on aquatic organisms exist. There are no studies indicating effects on organisms only exposed to DEHP via water, and at concentrations below the water solubility.

Long-term toxicity to fish

Atlantic salmon were fed with DEHP contaminated food with nominal concentrations of 0, 400, 800 and 1,500 mg/kg food (dwt). A 6% incidence of ovotestis in males, which was statistically significant compared to the control were no ovotestis was observed, occurred in the highest dose group (1,500 mg/kg dwt) after 4 month. After 9 month an incidence of ovotestis of 1% (not statistically significant) was observed. Also at 800 mg/kg ovotestis was observed both after 4 month and 9 months, however not statistically different from the control group. The findings indicate that the effects obtained are reversible as no significant effects were seen after 9 month but only after 4 month. It can be concluded that the LOEC from this study is 1,500 mg DEHP/kg and the NOEC is 800 mg DEHP/kg. Based on the results from both studies it is concluded that the NOEC for effects on sexual differentiation of Atlantic salmon is 800 mg/kg food.

7.1.1.2 Aquatic invertebrates

Short-term toxicity to aquatic invertebrates

Several reliable short-term studies on effects of DEHP on aquatic organisms exist. There are no studies indicating effects on organisms only exposed to DEHP via water, and at concentrations below the water solubility.

Long-term toxicity to aquatic invertebrates

Several reliable long-term studies on effects of DEHP on aquatic organisms exist. There are no studies indicating effects on organisms only exposed to DEHP via water, and at concentrations below the water solubility.

7.1.1.3 Algae and aquatic plants

Several studies exist, and although no effects were found, a NOAEC can not be determined based on them as there are methodological shortcomings.

7.1.1.4 Sediment organisms

Studies with sediment organisms showed no effects at 1,000 mg/kg dwt, the highest tested concentration.

7.1.1.5 Other aquatic organisms

7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

7.1.2.1 PNEC water

Short term and/or long-term effect studies, where the test organisms are exposed to DEHP via water, are available for fish, amphibians, aquatic invertebrates, algae, higher plants, and micro-organisms. However, there are no reliable long-term studies below the apparent water solubility of DEHP indicating effects on organisms exposed to DEHP in water. Therefore, it is not considered suitable to specify a chronic NOEC for organisms exposed via water.

Hence a $PNEC_{water}$ cannot be specified.

However, there are studies showing effects of DEHP when fish are exposed via the food. A NOEC of 160 mg/kg food (ww) can be derived from two studies where effects of DEHP (administered via food) on gonadal development of Atlantic salmon were found. TGD does not give any guidance on how to use results from studies were the test organisms have been exposed via the food only. However, as food probably is the most relevant exposure route for fish this NOEC will be used in the risk assessment. Applying an assessment factor of 10 leads to a $PNEC_{food}$ of 16 mg/kg (fresh food).

7.1.2.2 PNEC sediment

The available studies with sediment-dwelling organisms exposed to DEHP show largely varying results. Short-term and long-term tests with *Chironomus spp.* larvae did not result in any effect at the highest concentrations tested. For amphibians, a $NOEC_{sediment} > 1{,}000$ mg/kg (dwt) was obtained. The NOEC of > 1,000 mg/kg derived from the frog studies is chosen for the derivation of a $PNEC_{sediment.}$ Effect studies exist with organisms from three trophic levels. Therefore an assessment factor of 10 is used, resulting in a PNEC of >100 mg/kg (dwt).

7.2 Terrestrial compartment

7.2.1 Toxicity test results

7.2.1.1 Toxicity to soil macro organisms

There are four valid tests with soil organisms (earthworm (*Eisenia foetida foetida)* and collembolan *Folsomia fimetaria*), all showing no effects. From these studies a NOEC ≥ 130 mg/kg dwt is obtained.

7.2.1.2 Toxicity to terrestrial plants

The effects of DEHP on the germination and growth of *Triticum aestivum, Lepidium sativum and Brassica alba* were studied according to OECD guideline 208. No effects were seen at the highest concentration studied, giving a NOEC of > 130 mg/kg dwt.

7.2.1.3 Toxicity to soil micro-organisms

A few studies exist, but because of shortcomings they do not permit determination of a NOEC. However, a questionmark still exists regarding possible effects on soil microorganisms.

7.2.1.4 Toxicity to other terrestrial organisms

Toxicity to birds

For effects on bird reproduction there is a NOEC of 1,700 mg/kg_{food}, based on reproductive effects in hens at 10,000 ppm (10.000 mg/kg) and, in another study on hens, totally impaired egg laying at a dose of 5,000 ppm (5.000 mg/kg).

Toxicity to other above ground organisms

For exposure of mammals via the food a NOEC of 33 mg/kg_{food} for mammalian predators is determined, based on studies showing testicular damage in rats at 4.8 mg/kg/day in an oral three generation reproductive toxicity study (see section 5.9 for further details).

7.2.2 Calculation of Predicted No Effect Concentration (PNEC_soil)

The PNEC (> 13 mg/kg dwt) is derived from a study where no effects were seen in terrestrial plants at the highest tested concentration (NOEC>130 mg/kg dwt and using an assessment factor of 10). The other soil toxicity studies indicate even lower sensitivity and, thus, the actual PNEC may be higher.

7.3 Atmospheric compartment

No studies exist from which a $PNEC_{atmosphere}$ could be derived.

7.4 Microbiological activity in sewage treatment systems

7.4.1 Toxicity to aquatic micro-organisms

Only one study, on respiration in activated sludge, is considered valid for the risk assessment of DEHP in STPs. No effects were observed at the highest tested concentration, 2,007 mg/L (NOEC).

7.4.2 PNEC for sewage treatment plant

Only one study on respiration in activated sludge was considered valid for the risk assessment. The NOEC from this study was 2,007 mg/l (highest tested concentration). According to TGD, an assessment factor of 10 should be used on NOECs obtained from respiration tests. Hence, the $PNEC_{STP}$ is >201 mg/l.

7.5 Calculation of Predicted No Effect Concentration for secondary poisoning (PNEC_oral)

Effects on birds and mammal populations are rarely caused by mortality after short-term exposure. Therefore, results from long-term studies are preferred, such as NOECs for mortality, reproduction or growth.

For birds there is one study with results suitable for deriving a PNEC. This is the 28-day study with a NOEC of 1,700 mg/kg food for reproductive effects calculated from a LOEC of 10,000 ppm. Since it is a reproductive effect strictly applying TGD would lead to the use of an assessment factor of 10. However, there is also a long-term study (230 days exposure) in which egg laying was totally impaired at a dose of 5,000 ppm. From this study no NOEC can be derived but the results imply that a larger assessment factor than 10 is needed for the derivation of PNEC from the 28-day study. Therefore, an assessment factor of 100 is chosen resulting in a PNEC of 17 ppm (mg/kg). This PNEC is used in the risk characterisation for secondary poisoning of birds feeding on mussels in the EU RAR.

There are several studies on mammalians exposed to DEHP via oral exposure. In a continuous breeding study (chronic, > 90 days) on mice, Lamb et al. (1987; see RAR) found that 1,000 ppm DEHP produced a dose dependent and significant decrease in the number of litters as well as the number and proportion of pups born alive. The NOAEL was 100 ppm DEHP in food. Impairment of fertility is considered to be an ecologically relevant effect. Applying an assessment factor of 10 to the NOAEL from this study results in a PNEC of 10 ppm. Irreversible testicular damage was shown in male rats exposed *in utero* and during suckling at very low dose levels. The NOAEL was 4.8 mg/kg bw/day at a food concentration of 100 ppm (Wolfe et al., 2003; see RAR). According to TGD a food conversion factor of 3 should be applied, resulting in a $NOEC_{oral,\ mammalianss}$ of 100 ppm/3= 33.3 ppm. Finally, when applying the assessment factor of 10 (for chronic studies according to TGD) a PNEC of 3.3 ppm is obtained.

In conclusion, for the purpose of the EU risk assessment the $PNEC_{oral,\ mammalians}$ for non-compartment specific effects relevant to the food chain is set to 3.3 ppm (mg/kg food).

Summary of toxicity

Toxicity has been observed in fish, where DEHP affects the sexual differentiation (feminisation of males) after long-term exposure to DEHP via the food. The resulting $PNEC_{food}$ for fish is 16 mg/kg fresh food. DEHP also affects the reproduction of birds, with a NOEC of 1,700 mg/kg food, based on reproductive effects and impaired egg laying at doses > 5,000 mg/kg. In mammals, testicular toxicity is the most sensitive endpoint, with a NOEC of 33 mg/kg food for exposure of mammals via the food.

No effects have been observed in other aquatic or terrestrial species, and the derived PNECs are therefore based on the highest concentrations being tested and given as “larger than values”.

7.6 Conclusion on the environmental classification and labelling

There is no classification and labelling for the environmental compartment.

8 PBT, VPVB AND EQUIVALENT LEVEL OF CONCERN ASSESSMENT

8.1 Comparison with criteria from annex XIII

8.2 Assessment of substances of an equivalent level of concern

8.3 Emission characterisation

8.4 Conclusion of PBT and vPvB or equivalent level of concern assessment

INFORMATION ON USE, EXPOSURE, ALTERNATIVES AND RISKS

This section is mainly based on information which was available during the work with the risk assessment report (RAR) and risk reduction strategy (RRS). It is acknowledged that changes may have occurred in the volumes and use pattern.

DEHP is widely used as a plasticiser in polymer products, mainly PVC. Plasticisers have the function of improving the polymer material's flexibility and workability. DEHP is one of a number of substances used as plasticiser in PVC and other polymer materials. Examples of other plasticisers are other phthalates, adipates, trimellitates and phosphates.

The content of DEHP in flexible polymer materials varies but is often around 30% (w/w). Flexible PVC is used in many different articles e.g. toys, building material such as flooring, cables, profiles and roofs, as well as medical products like blood bags, dialysis equipment etc. DEHP is also used in other polymer products and in other non-polymer formulations and products. The wide use of DEHP gives rise to many possible scenarios of human and environmental exposure.

1 INFORMATION ON EXPOSURE

Release to the environment can occur during the production and industrial use of DEHP. The plasticiser can also be emitted from the finished material or article during its use and disposal. DEHP is not chemically bound to the PVC polymer matrix and can be released throughout the lifecycle of polymer products. The leaching rates may vary considerably between different products.

Occupational exposure may occur during the production and industrial use of DEHP. Consumer exposure to DEHP may occur via medical products and diffuse emissions from the use of articles containing DEHP. Human exposure via food, water and air may occur as a result of emissions to the environment from all life cycle stages.

Due to the long technical lifetime of some PVC products and the high persistency of the polymer material in the environment, emissions from products can continue for a long period of time. This may also include emissions from particles of the material entering the environment via wear etc.

Exposure of the general population to DEHP

The general population is mainly exposed to DEHP released from consumer products and via food.

Exposure via articles

Because plasticisers in flexible PVC and other materials are not chemically bound, they may be released from the finished article during its life-time. The routes of exposure will include inhalation, dermal and oral and possibly combinations of these routes. Some examples of the sources of exposure for different routes are:

- *inhalation* - release of DEHP from building materials (wallpaper, floor coverings etc.), home furnishing, car interiors etc.
- *dermal* - skin contact with footwear, rainwear, PVC gloves, artificial leather on furniture and car seats, toys etc.
- *oral route* – certain baby- and children's products and food contact materials

Exposure via food

Several studies show that DEHP occurs in dairy products, either because of presence in the cow milk or because of contamination of the milk from PVC-tubing during the processing or from food packaging. A 90th percentile concentration of 0,05 mg DEHP/kg cow milk was used in the RAR. The concentration in fish has been reported to be up to 2.3-2.6 mg/kg. DEHP has also been shown to occur in diet samples, baby food, and infant formulae. The highest concentration of DEHP in a Danish total diet sample was 0.49 mg DEHP/kg, which could result in an exposure to 16 µg DEHP/kg body weight/day for a person weighing 70 kg.

DEHP is also present in human breast milk. The mean (± S.D.) concentration of DEHP in milk from Swedish mothers was 17.1 ± 46.8 µg/liter milk. When also including the metabolite MEHP (mono(2-ethylhexyl)phthalate) concentration, the 95th percentile concentration was 47.3 µg/liter milk. For a newborn (0-3 months of age) a milk concentration of 47 µg/liter results in a daily exposure to 6.2 µg/kg/day of DEHP and MEHP. Exposure to DEHP via infant formulae was calculated to 13 µg/kg/day for 0-3 months old infants.

Assessment of total exposure

Based on the measured data on the presence of DEHP and it's metabolites in urine and the knowledge of the fraction of DEHP that is excreted in urine, the total daily intake of DEHP can be calculated. By this approach, an estimate of the total exposure is obtained, including the contribution from handling and processing the food. The calculated values would also cover exposure from articles, although the main contribution is believed to come via the food, at least for adults.

There are recent biomonitoring data on the excretion of DEHP-metabolites in urine of different populations in Germany and the US. Daily regional exposure to DEHP was estimated based on measured urinary excretion of DEHP-metabolites in a German population mainly made up of adults. When the urinary concentrations were recalculated by the rapporteur using the conversion factor of Koch et al. (2003d; see RAR), a 95th percentile intake value of 17 µg/kg/day was obtained.

However, there is considerable uncertainty in this value as it is based on a conversion factor obtained from a single exposure of one adult individual, and as there are indications from many studies that children may be exposed to 2-fold higher amounts of DEHP than adults (when calculated per kg body weight).

New data published after the RAR was finalised

After the RAR was finalised, additional studies looking at the human exposure to DEHP have been performed. These studies have not been thoroughly evaluated, but they will still be mentioned here. Overall, the impression is that the new studies appear to support the assessments done in the EU RAR. Thus, Fromme et al (2007a) have analysed diet samples and found a DEHP content in the food which would result in median and 95%-il daily intake in German adults of 2.4 and 4.0 µg/kg/day, respectively. Wittasek et al (2007a) measured urinary metabolites of DEHP in urine samples obtained from a German specimen bank for human tissues. The results seem to indicate a decreasing exposure to DEHP from 1988-2003, with a median exposure of adults to 2 µg/kg/day in 2003. Wittasek et al (2007b) also assessed the exposure of German children to DEHP, using two somewhat different approaches, and obtained median daily intake values of 4.3-7.8 µg/kg/day and 95%-il values of 15-25 µg/kg/day. However, as indicated by data from Fromme et al (2007b), the day to day variation in urinary excretion of DEHP is so significant that data based on 24 hours urinary samples (i.e., most if not all studies this far) are rather uncertain.

An overall assessment of all data shows that the general population is exposed to DEHP. The data seem to indicate 95%-il exposure levels in the range of 2-25 µg/kg/day, with the higher end representing children.

Production and use of DEHP

The European consumption of DEHP was calculated to 476,000 tpa in 1997. DEHP represented 51% of all phthalate plasticiser use. 97% of the DEHP consumption was used as a plasticiser in polymers, mainly flexible PVC. The remaining 3% was used in non-polymer applications such as adhesives and sealants, paints and lacquers, printing inks and capacitors. It was also used in advanced ceramic materials for electronic and structural applications.

Information made available by the manufacturers' trade organisation ECPI shows that the production and consumption of DEHP has decreased significantly since 1997, see Table 9.

Table 9: DEHP production and consumption (thousand tonnes) in 15 EU Member States plus Norway, Iceland, Switzerland, Turkey, Cyprus and Malta (pers.comm. D.Cadogan, ECPI, February 2005).

	1997	1998	1999	2000	2001	2002	**2003**	2004
Production	666	621	625	514	428	344	276	247
Consumption	476	492	467	422	359	308	248	221

Production and use of PVC plasticised with DEHP

DEHP is widely used as a plasticiser in polymer products, mainly PVC. Plasticisers have the function of improving the polymer material's flexibility and workability. The content of DEHP in flexible polymer materials varies, but is often around 30 % (w/w).

The main distinction between the numerous possible applications of PVC is between « rigid PVC » (accounting for about two thirds of total use) and « flexible PVC » (accounting for about one third). The use of plasticisers in rather high quantities constitutes a specific characteristic of PVC manufacturing compared to other types of plastics.

PVC is a thermoplastic material, i.e. upon heating it melts and can then be brought into many forms and shapes through various processes. After cooling, the material regains its original properties. A large number of different methods that use this principle are employed in the transformation of PVC, notably extrusion, calendaring, injection moulding, blow moulding, rotation moulding, thermoforming, and film blowing.

Statistics produced by the PVC industry estimate that the total PVC producing and transforming industry in Western Europe comprises more than 21.000 companies. The industry can be roughly divided into: PVC polymer producers, plasticiser producers and PVC transformers. PVC polymer is produced by a relatively small number of companies, mostly located in Europe, the US, and Japan. The transformation of PVC into final products, which requires two or three different manufacturing operations, is essentially done in more than 21,000 small and medium sized enterprises.

It is estimated that 6500 companies are involved in the flexible PVC value chain. Only about 800 of these are flexible PVC converting plants. The other companies use intermediates, are fabricators, wholesalers and installers.

DEHP is used to produce flexible plastics that are part of many products for both industrial and consumer use. These include building products (insulation of cables and wires, tubes and profiles, flooring, wallpapers, out-door wall- and roof covering, sealants and insulations), certain children's products, clothing (footwear, outwear and rainwear), car products (e.g. car under-coating, car seats made of imitation leather) etc. To further illustrate the widespread use of DEHP, articles like prams, shower curtains and textile prints could also be mentioned. Several products may have long technical lifetimes e.g. roofing materials (20 years), cables (30 to 50 years), flooring (20 years) while others have quite short service life.

The main part of the total DEHP consumption is used in indoor PVC applications such as flooring. The remaining part is used mainly in outdoor use that includes applications such as cables, roofing materials, coated fabrics and car undercoating.

Information from Japan Plasticizer Industry Association has been used to further describe the main plasticized PVC product categories in below (OECD, 2004).

Table 10 below (OECD, 2004).

Table 10: DEHP use applications and the main plasticized PVC products. Source: Study Group for Risk Assessment and Management of DEHP, 2003 as cited in OECD, 2004.

DEHP use category	Description of products
Films and Sheets	Generally, FPVCs with the thickness of 0.2 mm or more are called sheets, and what are thinner than sheets are called films. They are widely used for packing materials. They are also used in laminations for furniture and ornaments, covers of books and magazines, covers of electrical appliances and machines. There are also uses in toys, raincoats, umbrellas, shopping bags etc.
Green houses sheets	(Agrovinyl) They are used for green house cultivation of vegetables, fruits, etc. They are also used for aquaculture of eels etc. Recycling is particularly advanced in this field.
Synthetic leather	This is a FPVC product with cloth lining. It is used for furniture applications such as sofas, chairs and vinyl wardrobes. It is also used for tablecloths, table covers, accordion style curtains, etc. Further, it is used for interior materials of motor vehicles and in fashion such as belts, bags and briefcases.
Compounds	Raw materials for industrial uses: compound sol, or plastisol is made of minute powders of FPVC, dispersed in the liquid plasticizer in the form of colloidal matter. It is easy to mold, it can be fabricated into FPVC products with elasticity after being heated in processes such as spread painting, immersion, spraying and injection, half-fusion molding or rotation molding.
Wires and cables	A typical FPVC application. After the Second World War, the wires and cables using fire-resistant FPVC with self-fire-extinguishing nature spread quickly instead of rubber coverings that caused short circuit accidents by aging. Generally, FPVC is used for exterior sheaths (jackets) at large and low-pressure insulation, and is also used for the interior wirings or cords of home electric and electronic appliances.
Hoses and profiles	Hoses (gardening/agriculture/industrial), tubes (medical care/wheeled vehicles), flexible hoses (washing machines/cleaners), gaskets (construction/refrigerators). There are also industrial applications. It is also used as sealing material for sash

	windows and windows of motor vehicles.
Flooring	FPVC is used extensively for interior materials of buildings such as flooring and ceiling materials. Particularly, 90 percent or more of wallpapers are made from FPVC. FPVC material characteristics include flame-resistance, softness and light-weight, ease of design and construction. FPVC flooring may be tiles, long sheets or tile carpets. Further flooring materials are so-called cushion floors on which FPVC is made to foam.
Wall coverings	See **Flooring**
Paints and lacquers	DEHP is used also for paints, adhesives and pigments. It is used to help the formation of coating of vinyl acetate emulsion paints. For adhesives, it is used as an additive agent for carton boxes and plywood for furniture. Further, for pigments, it is used as an additive agent to toners.
Shoe soles	It is used for so-called chemical shoes, sandals, slippers, Japanese sandals, and injection boots.
Others	Mats, tapes, gloves, color fences, clothes hanger, erasers, for rubber, solvents,etc. Main FPVC applications for hospital use: blood bags, blood circuit of artificial kidneys or cardiopulmonary pumps and transfusion sets.

2 INFORMATION ON ALTERNATIVES

Several studies have been performed on alternatives to DEHP and other phthalates. This section provides a summary of information that was collected during the work with the Risk Reduction Strategy (RRS). In general, there is no single alternative suitable for all applications of DEHP. Instead a number of alternatives are available; such as other phthalates and other plasticisers. Other materials are also available that do not need additives to become flexible.

2.1 Alternative substances

A survey performed by the Swedish Chemicals Agency in 2000 showed that DEHP is mainly replaced with the other phthalates DIDP (Diisodecyl phthalate) or DINP (Diisononyl phthalate) on the Swedish market. Other alternatives in use to a lesser extent are adipates and trimellates. In Table 11 alternatives found in the survey for different applications are summarised.

Table 11: Alternatives in use in different applications

Application	Alternatives in use
Coil coated roofing	DIDP, polyurethane, polyester
Fabric coating	DIDP, DINP
Floor and wall coating	DINP, polyolefines
Cable	DIDP or other phthalates
Foil	DIDP
Profiles	DINP

Studies on alternatives that have been performed in Denmark, the Netherlands and by the organisation Health Care Without Harm are summarised below. Reference is also made to an opinion from the Scientific Committee on Toxicity, Ecotoxicity and the Environment and to the risk assessment conclusions from the Existing Substances Programme for the alternative phthalates DIDP and DINP.

Danish assessment of Alternatives to phthalates

In a report from the Danish EPA a range of alternatives to phthalates and to flexible PVC are assessed with respect to their inherent properties and potential risk for humans and the environment (Miljöstyrelsen, 2001).

One criterion for identifying plasticisers as possible substitutes for phthalates was that most of the information should be available for both health and environment. Other criteria were that their use pattern should involve high PVC volume and/or expected high exposure of humans and/or the environment.

In Table 12 identified alternative substances and materials for different applications are summarised.

Table 12: Identified alternative substances and materials in different applications

Application	Alternative substance/material
Cables	Di(2-ethylhexyl)phosphate Tri(2-ethylhexyl) phosphate Tri-2ethylhexyltrimellitate Akylsulfonic acid esters
Floor and wall covering	Butane ester Di(ethylhexyl) adipate Trimethyl 1,3-pentanediol diisobutyrate
Toys	Polyethylene
Printing inks	O-acetyl tributyl citrate Dioctyl sebacate
Fillers	Polyester Dipropylene glycol dibenzoate

Dutch study on alternatives for phthalates

The Dutch Ministry has commissioned a report designed to quickly analyse to what extent phthalates used in PVC can be replaced by alternative substances or by alternative materials (TNO, 2002). The study concentrates on an assessment of technical possibilities and an environmental comparison. The report concludes that in general there is a broad range of alternatives to most of the product groups with the exception of medical devices where legal quality rules apply.

In terms of risk reduction the report cautiously states that the use of benzoates and possibly citrates, instead of phthalates might have some benefits for human health and the environment. Another conclusion is that it is likely that the use of plasticisers that are known not to give rise to emissions will result in a significant reduction of risks. In Table 13 alternative substances and materials are listed.

Table 13: Alternative substances and materials

Application	Substance alternatives	Material alternatives
Flooring	Benzoates. Phosphates, trimellitates and alkyl sulphate derivate are suggested but not tested.	Linoleum, rubber, polyolefins, wood and textile (sometimes different functionalities)
Cables	Trimellitates and polymeric plasticisers	Polyethylene
Roofing	Alkyl sulphate derivate and polymeric plasticisers (inconclusive suggestions)	Tar/bitumen, chlorinated polyethylene and ethylene propylene rubber
Building plate	Polymeric plasticisers	Polyester
Car undercoating	Benzoates and alkyl sulphate derivate; part can be replaced by rape oil fatty acid methyl ester	Bitumen/rubber mix and polyurethane
Tarpaulins	Benzoates and alkyl sulphate derivate	Polyurethane, ethylene propylene rubber, rubber coated cotton, polyethylene and polypropylene
Coated fabrics	Poly ester plasticisers, benzoates, phosphates and other polymers	Polyurethane for artificial leather. Paper for wall paper. Polyethylene for foils and acrylates
Toys	Citrates and adipates	Polyethylene, Polypropylene and rubber
Medical devices	Trimellitates and citrates(?)	Some applications: polyethylene, glass and latex (gloves)

HCWH report on neonatal exposure to DEHP

Health Care Without Harm (HCWH) is a campaign for environmentally responsible health care. It consists of 319 organisations, healthcare institutions and associations in 29 countries. Members of the campaign are hospitals, nurses, environmental organisations, religious organisations, trade unions and patient groups.

Their report on neonatal exposure discusses two alternative ways to substitute DEHP in medical devices; by replacing PVC-products with PVC-free products or replacing DEHP with an alternative plasticiser (Rossi and Muehlberger, 2000). According to HCWH both PVC-free and DEHP-free products are available on the market for most of the medical applications of concern, e.g. for applications in intensive care units for neonates.

The primarily identified alternative plasticizers for medical products are citrates and trimellitates. Potential alternative plasticizers are also phosphates, benzoates and aliphatic dibasic esters. Alternative polymeric materials are ethylene vinyl acetate, polyethylene, polypropylene, polyurethane and silicone.

Furthermore, HCWH has published a report called "Preventing Harm from Phthalates, Avoiding PVC in Hospitals" (Ruzickova et al. 2004) where the occurrence of DEHP in different health-care products is assessed and alternative products presented. This report also presents a number of case studies where DEHP-containing medical products have been replaced by alternative products (see http://www.noharm.org/pvcDehp/issue).

Scientific Committee on Toxicity, Ecotoxicity and the Environment

The CSTEE has concluded in an opinion that there is no safety concern when young children are mouthing PVC-toys containing Acetyl Tributyl Citrate (ATBC) as plasticiser (CSTEE, 2004).

Risk assessments on DIDP and DINP in Existing Substances Programme

As can be seen from the information above, in some applications other phthalates are chosen to substitute DEHP. The most common alternative phthalates are DIDP and DINP. These two phthalates have also been assessed within the EU program on Existing substances (European Union Risk assessment Report on di-"isodecyl" phthalate and European Union Risk assessment Report on di-"isononyl" phtalate).

For DINP the risk assessment concluded that there was "no need for risk reduction measures" for consumer exposure. However, the SCTEE (Scientific Committee on Toxicity, Ecotoxicity and the Environment) could not endorse the conclusion. The SCTEE maintained that there are reasons for concern for child health related to this use of DINP. This disagreement cannot be resolved until new and unequivocal toxicological evidence is made available. In the case of DIDP, the risk assessment and the relevant opinion of the SCTEE concluded that DIDP would pose risks for child health under certain conditions if used in a way similar to DEHP and DINP as plasticizer in PVC toys. For the environmental scenarios the risk assessments concluded that there was no concern for DIDP or DINP. Neither DIDP nor DINP have been classified as harmful to health or to the environment under directive 67/548/EEC.

2.2 Alternative techniques

Substitution of DEHP with other substances and materials is not the only alternative. By inventing or using new technology the need for plasticising by using phthalates might decrease. Alternative technique on its own or in combination with other substitution activities might thus be a possible solution. One option for many applications could be substituting PVC with other polymers that do not need additives to be flexible.

Technology under development is formulation of PVC with other polymers like ethylvinylacetate (EVA) and polyurethane (PU). By this technique mixtures of PVC can be obtained with different flexibility without plasticisers.

Research about the possibilities to use phthalates fixed within the polymer and not as an additive that can migrate is also taking place.

3 RISK-RELATED INFORMATION

Due to the wide spread use and exposure to humans of DEHP and the ability of the substance to cause effects on fertility and foetal development, concerns were identified in the human health part of the RAR for a number of subpopulations.

Concerns were identified for children exposed to DEHP from toys and childcare articles.

From 16 January 2007 restrictions on the marketing and use of six phthalates apply (directive 2005/84/EC, now Reach annex XVII). The three phthalates bis (2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP) and benzyl butyl phthalate (BBP) shall not be used as substances or as constituents of preparations, at concentrations of greater than 0,1 % by mass of the plasticised material, in toys and childcare articles. Such toys and childcare articles containing these phthalates in a concentration greater than the limit mentioned above shall not be placed on the market.

The same restrictions apply to the three phthalates di-"isononyl" phthalate (DINP), di-"isodecyl" phthalate (DIDP) and di-n-octyl phthalate (DNOP) in toys and childcare articles **which can be placed in the mouth by children**.

The restrictions impact the use of DEHP and some common alternative phthalates in toys and childcare articles. However recent information shows that children may be exposed to DEHP in a similar way from other articles e.g. school supplies.

Concerns were also identified for patients exposed via medical devices and for workers in production and industrial use of DEHP and products containing DEHP. Further, concerns were identified for children exposed via the environment near industrial point sources.

In addition, the risks from indirect exposure via the environment of all humans, from many different sources, were highlighted although never quantified in the risk assessment. It has been described as a continuous low dose exposure of all humans. The risk assessment suggests that outdoor applications of polymers plasticized with DEHP like roofing, coil coating, coated fabric, hoses, profiles, car undercoating and shoe soles give rise to the major part of DEHP emissions.

In the environmental assessment of the RAR, the available information indicated concern in some local scenarios for soil and sediment organisms, but it was acknowledged that further information could remove the concern. However, as there was concern for mammals eating worms, and for birds eating mussels in the same local scenarios, no further information was asked for in the light of the risk reduction measures that anyway would be needed to limit the risks for secondary poisoning of mammals and birds in these local industrial scenarios.

Other indications that emissions and exposure of DEHP causes concern have recently been mentioned:

- Several RAPEX notifications of national activities/regulations for limiting the use of DEHP in different products because of concern for the health of children using these products (65 notifications as from 2005; http://ec.europa.eu/consumers/dyna/rapex/create_rapex_search.cfm).
- DEHP has been identified as a priority substance under the Water Framework Directive and therefore an environmental quality standard (EQS) has been proposed by the European Commission (http://eur-lex.europa.eu/LexUriServ/site/en/com/2006/com2006_0397en01.pdf). Research in the UK has shown that emissions from new housing estates could be the source of DEHP released to the sewage system and eventually ending up in surface waters at concentrations that may exceed the EQS.

In the EU RAR, the exposure of the general population was assessed by different approaches. For exposure of newborns via breast milk or infant formula, the 95-%il exposure levels were shown to be 6 and 13 ug/kg/day, respectively. However, additional exposure from other sources is likely to exist (e.g., ingestion of indoor dust, inhalation of indoor air, and through direct dermal contact with different articles), although it was not quantified.

The exposure of adults was estimated via analysis of DEHP-metabolites in urine. The advantage of this approach is that it includes exposure from all possilbe sources (e.g. via food and from articles). Although uncertain, a 95-%il exposure level of 17 ug/kg/day was agreed for the general population, and it was acknowledged that many studies indicate that the exposure of children is higher than for adults. However, the exposure of children was not quantified.

Studies performed after the RAR was agreed (and thus not evaluated and discussed by the Technical Committee on New and Existing Substances, TC NES), indicate 95-%il exposure levels of 2-25 ug/kg/day for the general population, with adults in the lower end and children in the higher end of this range.

When comparing the currect exposure levels with the DNELs calculated in this dossier, it is notable that the exposure of adults is below the proposed DNEL (perhaps by a factor of 10), whereas the 95-%il exposure of children may be similar or higher than the proposed child DNEL.

OTHER INFORMATION

Extensive consultations with industry and member states experts took place during the risk assessment (1996-2006) and the preparation of a strategy to limit risks (2004-2006) under regulation (EEC) 793/93, including written communication, bilateral meetings with representatives of industry producing and using DEHP, and discussions in meetings (meetings of Technical Committee of New and Existing Substances, TCNES, and Risk Reduction Strategy Meetings RRSM). The results from these consultations have been incorporated in the Risk Assessment Report and the Strategy to Limit Risks.

REFERENCES

This Annex XV dossier mainly builds on the agreed European Union Risk Assessment Report (RAR) on DEHP performed under regulation EEC 793/93 and the corresponding European Union Risk Reduction Strategy (RRS). Information from those documents is used in this dossier without giving full references in the dossier. Thus, the reader is referred to the RAR and the RRS (the latter is attached to this dossier). New information and new studies not used in the RAR and RRS are given as full references in the dossier.

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ANNEX

EU Risk Reduction Strategy on DEHP (ES 37b-2004).

Figure 1 vbvnbv

Example 1 hff

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