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**Scientific Committee on Toxicity, Ecotoxicity and the Environment**
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# SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

## Opinion on the results of the Risk Assessment of:

## Bis (2-ethylhexyl) phthalate (DEHP)

**CAS No.: 117-81-7**

**EINECS No.: 204-211-0**

**REPORT VERSION (Human Health)**
**September 2001**

**Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]**

**Opinion expressed at the 29th CSTEE plenary meeting**

**Brussels, 09 January 2002**

[1] Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94, which is supported by a technical guidance document.

# Terms of reference

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

1. Does the CSTEE agree with the conclusions of the Risk Assessment Report?

2. If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

## INTRODUCTION

DEHP is widely used as a plasticiser in polymer products, mainly PVC. Flexible PVC is used in many different articles such as toys, flooring, cables, profiles, roofs, blood bags and dialysis equipment. DEHP is also used in other polymer products and in other non-polymer formulations and products. The production volume in Western Europe was 595,000 tonnes in 1997, of which 186,000 tonnes were exported. The import was estimated to 67,000 tonnes.

## GENERAL COMMENTS

The human health part of the DEHP RAR is in general of very high quality. The CSTEE agrees with the conclusion iii) for most worker exposure scenarios and for exposure of children consumers from toys and child-care articles. The CSTEE further supports the conclusion iii) for exposures from medical equipment and that there may be concern for several local indirect exposures of adults and children via the environment.

The CSTEE does not agree with the RAR that the study of Arcadi et al. (1998) is of a good enough quality to be used as the critical study for risk characterisation of developmental effects. Also, the CSTEE finds that the DEHP exposure estimates for indoor environments are exaggerated. In addition, the assignment of a higher bioavailability in young children compared to adults is not supported.

## SPECIFIC COMMENTS

### Exposure assessment

**Occupational**

Workers may be exposed to DEHP during production, industrial use of DEHP as an additive in formulation and processing of products, as well as industrial end-use of products containing DEHP. Worst case exposure concentrations during production is estimated to be 5 mg/m$^3$ (8 h TWA) and during industrial use of DEHP and industrial end-use of products containing DEHP 10 mg/m$^3$. Estimated internal exposures have been calculated to be 0.53 mg/kg/day via inhalation and 0.46 mg/kg/day via dermal exposure. Comparable figures for industrial use of DEHP are 1.06 and 0.3 mg/kg/day, respectively, and for industrial use of end products containing DEHP 1.06 and 0.928 mg/kg/day, respectively.

**Consumers**
Consumer exposure to DEHP may come from toys and child-care articles, building materials and home furnishing, car interiors, clothing and via medical devices and food contact materials. The criteria used by the CSTEE for calculation of oral exposure of children using DEHP-containing toys have been used. However, the RAR adjusts for alleged differences in oral bioavailability between children aged 0.5-3 years and adults (100 per cent vs. 50 per cent). The RAR uses the same exposure level of 200 mg/kg/day as was used by the CSTEE, but this is correlated to an internal NOAEL adjusted by 50 per cent availability, which was not done by the CSTEE. Dermal exposure in infants has been estimated to be 9-12.4 μg/kg/d.

For indoor air exposure, the RAR uses the air concentration at saturated vapour pressure (5.3 $\mu g/m^3$) as a worst case. Since there are indications that 3-fold more of DEHP can bind to dust particles, the total air concentration is estimated to be 21.2 $\mu g/m^3$. This is converted to a dose of 4.4 μg/kg/day in adults and 22.4 μg/kg/day in children. Calculated exposure to DEHP from car interiors are 0.9 and 2 μg/kg/day in adults and children, respectively. The exposure figures have incorporated assumed bioavailability of 75 per cent in adults and 100 per cent in infants/children.

The assignment of a worst-case of saturated vapours of DEHP being present in indoor environments is obviously an exaggeration and is not borne out by measured data. A number of measurements have shown indoor air levels which are only 0.1 to 5 percent of the default value used in the RAR.

Dermal exposure due to use of plastic gloves containing DEHP has been estimated to 6.7 μg/kg/day.

Exposures to DEHP from medical products may be very high (3.1 mg/kg/day in adults undergoing long-term haemodialysis and 1.7 mg/kg/day after transfusions to neonates).

**Indirect**
Low-level exposure to DEHP occurs due to diffuse contamination of food. The highest exposures identified are for infants exposed via infant formulae and breast milk, calculated to be 8-21 μg/kg/day (internal exposures).

**Combined exposure**
Combined worker internal exposures during production of DEHP has been estimated to 0.99 mg/kg/day, during industrial use of DEHP 1.36 mg/kg/day and from industrial end use of products containing DEHP 2 mg/kg/day.

Combined internal exposures via inhalation and dermal routes from indoor air, gloves and car interiors have been estimated to be 0.012 mg/kg/d in adult consumers.

In children consumers combined internal exposures from multiple pathways have been calculated to be 0.234 mg/kg/day.

## Effects assessment

### Toxicokinetics

An important premise in the RAR for risk characterisation for infants/children is the assignment of 100 per cent systemic oral bioavailability in young children in comparison to 50 per cent in adults. There are no oral absorption data from human infants. An experiment with 2 adult male volunteers showed an urinary elimination of 15-25 per cent of DEHP given orally at 10 mg/day for 4 days, in another experiment 1 adult volunteer eliminated 31 per cent of a single oral dose of 66 mg in the urine.

Several experiments with rats given DEHP orally at doses from 1.2 mg/kg up to 2000 mg/kg show that 42-69 percent is excreted in the urine, most studies show approximately 50 per cent urinary excretion. This constitutes the basis for assigning 50 per cent oral availability of DEHP in adults. Almost all of the remaining dose of orally administered DEHP in rats is recovered in the faeces. Very little parent compound is detected in the urine, since DEHP is rapidly hydrolysed in the intestine to MEHP and further metabolised after absorption. Faeces contains the parent compound and in addition a number of metabolites, some of which may be due to biliary excretion after systemic absorption. Experiments with cannulated rats show biliary excretion of 5-10 per cent of an oral dose. Thus, it is conceivable that up to 70 per cent of an oral dose of DEHP could be absorbed from the intestine in rats.

An adjustment factor of 2 is used for bioavilability of DEHP in children 0.5-3 years of age based on information from a study in rats (Sjöberg et al., 1985). These authors reported a significantly higher AUC, but not $C_{max}$ for MEHP in 25-day old animals, compared to 40- and 60-day old animals. However, this experiment was performed at a very high single dose of DEHP (1000 mg/kg), a dose at which DEHP hydrolysis appears to become saturated in rats. Thus, it is difficult to support the use of the bioavailability adjustment factor of 2 based on the Sjöberg et al. (1985) study.

Two experiments in rats examining dermal absorption indicate that approximately 5 per cent of the applied dose are excreted in urine and faeces by this route of administration. Two *in vitro* studies comparing permeability of DEHP with human and rat skin give conflicting results. In one experiment the permeability constant is 4 times higher with rat skin compared to human skin, whereas in the other experiment it is exactly the opposite. The CSTEE agrees with the RAR in using the level of 5 per cent bioavailability for dermal exposure.

The use of 75 per cent bioavailability of an inhaled dose of DEHP is supported by results of inhalation studies in rats.

### Acute toxicity

DEHP has a very low acute toxic potential by the oral and inhalation route. Acute toxicity studies by the dermal route are lacking, but the toxic potential by dermal exposure must also be very low when factoring in the low dermal bioavailability.

### Irritation

DEHP is a slight skin and eye irritant and there are some indications of respiratory lesions after inhalation of high air concentrations.

**Sensitisation**
There are no indications that DEHP is a skin sensitiser in animals or humans. There is no clear evidence that DEHP causes respiratory sensitisation, although a study of human infants indirectly linked bronchial obstruction to the presence of DEHP from PVC in floors.

**Repeated dose toxicity**
Only repeated dose studies of DEHP by the oral route are adequate for risk assessment. Critical organs in laboratory animals are the liver, kidney and testis. Repeated dose treatment of rats and mice leads to hepatomegaly due to increased hepatocyte proliferation and peroxisome proliferation. These effects are mechanistically linked to the presence of the peroxisome proliferator-activated receptor alpha (PPAR-α) in the liver. There are marked species differences in the PPAR-α-mediated effects of DEHP, so that the hepatotoxic effects of DEHP noted in rodents are not judged to be relevant for humans.

The RAR assigns a NOAEL for kidney toxicity of 28.9 mg/kg/d in males and 36.1 mg/kg/d in females from a 2-year study in rats (Moore, 1996) based on increased absolute and relative kidney weight. The CSTEE is in agreement with these values, although the critical effect for risk characterisation is testicular toxicity (*vide infra*).

Testicular toxicity has been noted in a number repeated-dose experiments in rats and mice. In a 90-day study in rats, dose-dependent Sertoli cell vacuolation was demonstrated with a NOAEL of 3.7 mg/kg/d (Poon et al., 1997). The CSTEE has previously used this NOAEL value in its opinion of 26/27 November 1998 and recommends to use this value also in the present context.

The RAR on DEHP uses *i.a.* effects on the kidney and the testis observed in rats as critical endpoints for extrapolation to humans. Two studies point to the possibility that rodents may not be ideal models for these endpoints. In 12-15 month old marmosets exposed to DEHP at levels of 100, 500 and 2500 mg/kg/day for 13 weeks, no testicular or other effects were observed (Kurate *et al.*: Toxicol. Sci. 42, 49-56, 1998). However, the possibility exists that younger animals may be more sensitive towards testicular toxicity (as in rodents) than the animals used in this study. In knock-out mice lacking PPARα, kidney and testicular toxicity was less pronounced after feeding of a diet containing 12000 ppm DEHP for 4, 8 and 24 weeks compared to wild-type mice (Ward *et al.*: Toxicol. Pathol. 26, 240-245, 1998), indicating the involvement of the receptor in part of the effects in kidney and testis.

**Carcinogenicity**
DEHP has been shown to induce hepatocellular tumours in six experiments in rats and 2 experiments in mice after long-term dietary administration. However, the mechanism involved in DEHP carcinogenicity in rodents (activation of PPAR-α) is not relevant to humans (IARC, 2000). There are some indications that DEHP may induce Leydig cell tumours and mononuclear cell leukaemia in rats. However, there are deficiencies in the reporting (Leydig cell tumours) and the relevance for humans is not readily apparent (mononuclear cell leukaemia). Taken together, DEHP does not fulfil the criteria for classification as a carcinogen.

**Mutagenicity**
DEHP has been studied extensively for its genotoxic effects in a wide range of test systems, both *in vitro* and *in vivo*. The majority of these studies did not reveal any activity. The CSTEE supports the RAR that the data on genotoxicity do not suggest a classification of DEHP.

**Reproductive toxicity**
A very recent well conducted and reported 2-generation reproduction study of DEHP in rats (Schilling *et al.*, 2001; CSTEE/2001/25-Add.3) has documented effects on reproductive performance and fertility in the F0 and F1 parental animals at 1088 mg/kg/d. Substance-induced signs of adverse developmental toxicity were noted in the progeny of the F0 and F1 parents from 340 mg/kg/d onwards. The NOAEL for reproductive performance and fertility was 340 mg/kg/d and for developmental toxicity 113 mg/kg/d, respectively.

In a continuous breeding study in mice, DEHP has been shown to decrease fertility both for males and females at 200 mg/kg/d and higher (Lamb *et al.*, 1987). A NOAEL of 20 mg/kg/d was identified in this study.

As noted above, testicular toxicity has been seen in a number of studies in rats and mice. Developing males have been shown to be more sensitive towards DEHP-induced testicular toxicity than sexually mature animals. Especially the study of Arcadi *et al.* (1998) has noted serious and irreversible testicular effects after exposing rats pre- and post-natally to DEHP in drinking water. A LOAL (a NOAEL was not identified, but preliminary experiments suggested that this was 5-fold lower) of approximately 3.5 mg/kg/d from this study has been used for risk characterisation for developmental toxicity. Although the results of this study clearly are of relevance, it is difficult to use this study as the critical one, since there are obvious limitations in the conduct and reporting. DEHP was diluted in the drinking water but no recording of water intake was performed. Also, there were no measurements of the DEHP concentrations in the drinking water administered to the animals assuring that the reported concentrations were correct. Further, the findings of the Arcadi *et al.* (1998) study are not supported by the findings of the very good 2-generation study of Schilling *et al.* (2001). Thus, it is scientifically difficult to accept the Arcadi *et al.* (1998) experiment as a definite study for risk characterisation. Instead, the CSTEE supports the NOAEL of 20 mg/kg/d for developmental toxicity from the Lamb *et al.* (1987) study.

**Endocrine effects**
Very high concentrations of DEHP (1 mM) may interact with the oestrogen receptor *in vitro*, but it does not induce estrogenic activity in *in vitro* yeast screens or *in vivo* in the rat uterine assay. On the other hand, there are indications that very high doses of DEHP *in vivo* may induce weak anti-androgenic effects.

## Risk characterisation

The RAR refers to the table 4.1.3.1.5 when it applies the various NOAELs/LOALs for the calculation of MOS values. From the above description it is clear that the CSTEE supports the values given in the table, but with two important exceptions. Firstly, the CSTEE does not agree to the use of a modification factor for oral bioavailability that is later used to differentiate between young children and adults. Secondly, the developmental LOAEL of < 3.5 mg/kg/d is not supported. The CSTEE recommends to use the same NOAEL for developmental toxicity as for fertility, namely 20 mg/kg/d.

**Workers**
The CSTEE agrees with the conclusion iii) for production of DEHP, industrial use of DEHP and industrial end use of products containing DEHP.

**Adult consumers**
The CSTEE agrees with the conclusion ii) for exposure from indoor air (although the exposure estimates are overerestimated), car interiors and multiple pathways of exposure.

**Children consumers**
The CSTEE agrees with the conclusion iii) for oral DEHP exposure from toys and child-care articles since the MOS for testicular effects will be well below 100 (20, rather than the reported 10), also when the correction for differences in bioavailability is not taken into account. However, the CSTEE disagrees with the conclusion iii) for testicular effects from inhalation, since the exposure calculations are highly exaggerated.

**Medical equipment**
The CSTEE supports the conclusion iii) of the RAR.

**Man indirectly exposed via the environment**
The CSTEE agrees that there appears to be concern for testicular effects, but not developmental effects, in adults for several local exposure scenarios. However, it must be emphasised that these conclusions are highly based on modelled data, so the exposure assignments are quite uncertain. This reservation holds true also for the assessment of children exposures. The CSTEE concludes that there may be concerns for testicular effects from regional exposures and for testicular and fertility effects, but not RTD effects, from some local exposure scenarios.

The CSTEE does not agree with the RAR that there is a need for limiting the risks from consumption of infant formulae, since the MOS values are above 300 when the proposed correction factor for bioavailability in young children is not taken into consideration. A similar view [conclusion ii)] pertains to DEHP exposure via breast milk.

**Combined exposure**

The CSTEE agrees with the conclusion of the RAR that characterisation of combined exposures indicate reasons for concern in some instances. As pointed out, assessment of combined exposures is difficult, since quantitative results for combined populations are lacking.