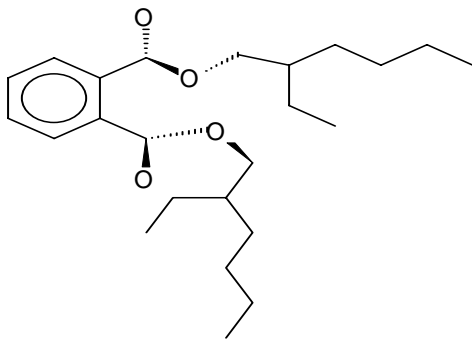


SIDS INITIAL ASSESSMENT PROFILE

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|---------------------------|--|
| CAS No. | 117-81-7 |
| Chemical Name | Bis(2-ethylhexyl)phthalate |
| Structural Formula |  |

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Bis(2-ethylhexyl)phthalate (DEHP) is readily absorbed and distributed in the body, but there is no evidence of accumulation. 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-EH (2-ethylhexanol). The substance is excreted via the urine, mainly as MEHP-metabolites, but some excretion via bile also occurs in rodents. Additionally, there are animal and human data showing that DEHP is transferred to mothers' milk. The relative extent to which different metabolites are produced and excreted is very complex and may depend upon the species, the age of the animal, sex, inter-individual differences, nutrition state, prior exposure to DEHP, the amount of DEHP administered, and the route of administration.

Acute toxicity studies indicate a low acute toxicity of DEHP. The oral LD₅₀ is >20,000 mg/kg b.w in rats and >10,000 mg/kg bw in mice. An inhalation LC₅₀ of about 10,600 mg/m³ for 4 hours in rats has been reported. Although there are no adequate acute dermal toxicity data, a low acute dermal toxicity is assumed.

Animal studies performed to current guidelines have shown a slight skin and eye irritation after administration of DEHP, but DEHP is not corrosive to the skin or eyes. DEHP has not been found to induce skin sensitisation in animals.

Numerous studies have investigated the toxicity of DEHP following repeated oral administration to experimental animals. Critical organs for DEHP-induced toxicity in laboratory animals are the **testis** (see below) and the **kidney**. The effects on the kidneys include increased: absolute and relative kidney weights, incidence and severity of mineralization of the renal papilla, incidence of tubule cell pigments, and incidence and/or severity of chronic progressive nephropathy. The lowest NOAEL for kidney toxicity is 29 mg/kg/day in the males and 36 mg/kg/day in females, derived from a chronic 2-year study in rats. In the liver, hepatomegaly due to hepatocyte proliferation, peroxisome proliferation and hepatocellular tumours are observed in experimental animals, but the hepatic effects are not believed to be relevant for humans.

Concerning the genotoxicity of DEHP, several different short-term tests, comparable to guideline studies and performed according to GLP, are available. The results are negative in the majority of the *in vitro* and *in vivo* studies performed with DEHP and its metabolites for detection of gene mutation, DNA damage, and chromosomal effects.

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Some positive results are obtained in the in vitro test systems which are also sensitive to several non-mutagenic substances. Overall, taking all data into account, DEHP and its major metabolites can be considered as non-mutagenic.

In rodent studies, liver tumours, Leydig cell tumours, and leukaemia have been observed. The liver tumours are most likely caused by peroxisome proliferation, and are therefore not considered relevant for humans. As to the other two tumours types, a relevance to humans can not be ruled out, although the evidence is inconclusive for this endpoint.

A conservative NOAEL value of 4.8 mg/kg/day has been set for testicular toxicity, based on a three-generation reproductive toxicity study, showing a low incidence of small male reproductive organs and minimal testis atrophy at 14 mg/kg/day and complete atrophy and aspermia at doses of 359 mg/kg/day. Developing and prepubertal rats have been found to be more sensitive to the DEHP-induced testicular toxicity than adults, and the NOAEL for testicular toxicity is therefore also used for developmental toxicity (4.8 mg/kg/day). Studies indicate that DEHP may also interfere with the male endocrine function and also influence the male sexual development. Testicular toxicity and developmental toxicity, observed in different animal species and at relatively low dose levels are considered relevant to humans. Effects on fertility has been observed at slightly higher exposure levels in mice and rats, with a NOAEL of 20 mg/kg/day observed in mice.

Environment

DEHP is a colorless liquid at room temperature. The vapour pressure is estimated to 3.4×10^{-5} Pa at 20°C. A large range of values on the water solubility (0.0006 – 1.3 mg/L at 20-25°C) is available in the literature. The probable explanation is that DEHP easily forms more or less colloidal dispersions in water. An estimated value of 0.003 mg/L was used for non-colloidal solubility. The Henry's law constant for DEHP is 4.43 Pa m³/mol. The octanol-water partition coefficient, log K_{ow}, is 7.5. However, in the model calculations the highest recommended value of 7.0 is used.

DEHP enters the environment mainly via direct release to air, from sewage sludge and from solid waste. In air, DEHP may occur both in vapour phase and as solid particles. The nature of these particles can be either aggregated pure DEHP or polymer particles containing DEHP. The log K_{oc} for DEHP is 5.2 L/kg. Hence, DEHP will be strongly adsorbed to the sludge, in sewage treatment plants. Particles formed by weathering of polymer products probably represent an important route of DEHP distribution.

Photodegradation of DEHP (reaction with OH radicals) is important in the atmosphere ($T_{1/2}=1$ d) but is assumed to be of little importance in water and soil. DEHP does not hydrolyse in water. The biodegradation of DEHP is varying in available studies. Based on the results of standard biodegradation test DEHP is rapidly biodegradable. Experimental data indicate biodegradation half-life for DEHP in surface water of 50 days, and 300 days in aerobic 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.

DEHP is found to bioaccumulate in aquatic organisms, and the highest BCF values are observed for invertebrates, e.g. 2700 for *Gammarus* (BCF_{fish} 840). This indicates that uptake via the food chain might be an important exposure route (secondary poisoning). BCF 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. For exposure via the food a NOEC of 33 mg/kg_{food} for mammalian predators is determined, based on studies showing testicular damage in rats. For effects on bird reproduction a NOEC of 1700 mg/kg_{food} is calculated.

Several reliable short-term and 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. However, effects have been shown on fish exposed to DEHP via food. Therefore a NOEC for fish of 160 mg/kg_{food} has been determined. Studies with sediment organisms showed no effects at 1000 mg/kg dwt, the highest tested concentration. 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, 2007 mg/L (NOEC).

There are four valid tests with soil organisms, from three trophic levels, all showing no effects. From these studies a $\text{NOEC} \geq 130 \text{ mg/kg dwt}$ is obtained.

The large amount of DEHP accumulated in the technosphere indicates a considerable potential for formation and distribution of MEHP. However, the formation rate and fate of MEHP in the environment is not known. MEHP causes reproductive toxic effects in studies on mammals. There are no other data on ecotoxicological properties of MEHP available.

There is a Priority Substance List Assessment Report Bis(2-ethyl hexyl) Phthalate produced by Canada in 1994 (<http://www.ec.gc.ca/substances/ese>).

Exposure

The global production of DEHP in 1994 was estimated to be between 1 and 4 million tonnes per year. The production volume of DEHP in Western Europe was 595,000 tonnes per year in 1997.

The main use of DEHP is as a plasticizer in polymer products, mainly in flexible PVC. 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 in medical products like blood bags, dialysis equipment etc. DEHP is also used in other polymer products and in non-polymer formulations and products. This implies multiple sources of DEHP emissions. The main part of DEHP emissions originates from use and disposal of polymer products. These emissions are widely dispersed, and monitoring data of DEHP in environmental samples confirm a widespread occurrence.

Occupational exposure to DEHP, mainly through inhalation but also via the dermal route, occurs in the production of DEHP, industrial use of DEHP as an additive, and at industrial end-use of semi-manufactured products and end-products containing DEHP. The general population can be divided into sub-populations, as the extent of exposure is expected to be different in different sub-populations (e.g. adults, young/children), partly caused by a suspected higher bio-availability of DEHP in children than in adults. The exposure can be via many different sources, such as indoor air, car interiors, toys, medical equipment, and indirectly via the environment or via breast milk. Due to the multiple pathways of exposure, the combined exposure should be considered. Urinary biomonitoring of the total human exposure to DEHP has shown considerable exposure.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical possesses properties (testis, kidney, and reproductive toxicity) indicating a hazard to human health. Due to the widespread use of the substance, leading to continuous exposure at low level, member countries are invited to perform an exposure assessment, and if necessary, a risk assessment for human health.

Note: A risk assessment performed in the European Union in the context of the EU Existing Substances Regulation reveals concern for several toxicological endpoints in occupational settings, but also for consumers as a consequence of use of toys and some medical technical equipment. In addition, there are concerns for effects on humans via the local environment outside plants producing or using DEHP.

Environment: Based on the chemical's properties (bioaccumulation, effects in fish after dietary exposure and the low NOAEL for reproductive toxicity) member countries are invited to perform an exposure assessment specifically investigating secondary poisoning.