

# Overview

## Background and scope of the assessment

Diethylhexyl phthalate (DEHP) (CAS No 117-81-7) was declared as a Priority Existing Chemical (PEC) for public health risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) on 7 March 2006. The decision for declaration was based on

- ubiquitous use of phthalates including DEHP in industrial and consumer products
- consumer products being significant sources of repeated and long term exposure of the public to DEHP through migration and leaching from products
- the potential for adverse health effects, particularly reproductive effects from DEHP exposure, especially in certain subpopulations
- current restrictions overseas for the use of DEHP in certain consumer products.

The purpose and scope of this PEC assessment is to determine the risks to adults and children from DEHP in consumer applications with particular potential for repeated or prolonged exposure, such as adult cosmetics and children's toys and child care articles.

## Manufacture and importation

Data collected through calls for information specific for the assessment of DEHP and for other purposes (e.g. compiling the High Volume Industrial Chemicals - HVIC list) suggest that most of the DEHP introduced in Australia (excess of 2500 tonnes in 2004; between 10000 and 99000 tonnes in 2006) is for industrial applications. DEHP is imported in finished products or mixtures and as a raw material for local manufacture. Manufacture of DEHP as a raw material was not reported.

The amount of DEHP used for applications with the potential for public exposure, such as toys, childcare articles and cosmetics is likely to be significantly lower. One applicant who imports DEHP as a raw material that may be used in these specific applications indicated importation volumes of approximately 67 tonnes in 2005 and 60 tonnes in 2006.

## Uses

Information on worldwide use of DEHP indicates that while it is used ubiquitously as a plasticiser for PVC for a variety of applications, significant restrictions have been implemented on its use in toys, childcare articles and cosmetics in Europe and USA.

The information collected by NICNAS identified that in Australia DEHP is imported as a component of perfumery and cosmetic products of unidentified origin with typical concentrations of approximately 0.05%. Some businesses indicated phasing out of DEHP in cosmetic applications following the ban of DEHP for use in cosmetics in the European Union (EU). However, given the absence of regulatory measures limiting the use of DEHP in cosmetics in Australia its potential use in these applications cannot be excluded.

The information also suggests that currently the use of DEHP in children's toys and childcare articles in Australia is limited. However, given the absence of regulatory measures restricting DEHP use in these applications, the potential for introduction and use of DEHP in children's toys and childcare articles in Australia cannot be excluded.

## NICNAS Draft Report for Public Comment

DEHP is used ubiquitously in Australia in a range of industrial and consumer applications mainly as a plasticiser (plastic softener) for polyvinyl chloride (PVC) products but also in other polymers for coatings, adhesives and resins. It is one of a closely related group of phthalate esters, which, in many cases, can be mixed or substituted for each other in individual applications.

### Health effects

DEHP is rapidly and almost completely absorbed following oral or inhalation exposure. A bioavailability of 100% is assumed for these routes. In contrast, bioavailability via dermal absorption is not likely to exceed 5%.

DEHP has low acute toxicity via all routes and low skin and eye irritation potential. There is no evidence of skin sensitization for DEHP in animals or humans.

Repeated exposure to DEHP in rodents is associated consistently with adverse effects on the liver (hepatomegaly, peroxisome proliferation and hepatocellular tumours), kidneys (increased weights, mineralisation of renal papilla, tubule cell pigments and chronic progressive nephropathy) and the reproductive system mainly in males (organ toxicity following pre and postnatal exposure resulting in fertility and developmental effects). Mononuclear cell leukaemia (MCL) and Leydig cell tumours were also observed inconsistently in rat studies.

The major molecular mechanism underlying hepatotoxicity of DEHP in rats and mice involves activation of peroxisome proliferator activated receptor alpha (PPAR $\alpha$ ), a mechanism that is not considered relevant for humans. MCL is not found in other mammalian species and has no comparable type in humans. Consequently, the liver effects and MCL observed following DEHP exposure in rodents are regarded to be species specific and not relevant to humans.

The mechanism underlying renal toxicity of DEHP is not clear but does not appear to be related to peroxisome proliferation as kidney lesions were found in both PPAR $\alpha$ -null and wild-type mice. Therefore, the relevance of this effect to humans cannot be excluded. The LOAEL for kidney toxicity (increases in absolute and relative kidney weights) in a well conducted 104-week rat dietary study was 146.6 mg/kg bw/d. The NOAEL was 28.9 mg/kg bw/d.

Testicular toxicity manifests as decreased testes weights, testicular atrophy, increased bilateral aspermatogenesis, immature or abnormal sperm forms, seminiferous tubular degeneration, Sertoli cell vacuolation or complete loss of spermatogenesis. The LOAEL for testicular effects is established at 3.7 mg/kg bw/d based on increased incidence of Sertoli cell vacuolation in a 13-week rat dietary study. The NOAEL is 37.6 mg/kg bw/d.

Multigenerational studies with rodents reveal adverse reproductive effects of DEHP manifesting as decreased fertility and adverse developmental effects on progeny.

A LOAEL for effects on fertility is established at 140 mg/kg bw/d based on decreased number of litters and viable pups in the progeny of adult mice treated with DEHP for 14 weeks starting 7 days pre-mating. The NOAEL is 14 mg/kg bw/d. Fertility of both sexes was affected as demonstrated by a cross-over mating trial at the highest dose of 425 mg/kg bw/d. Interestingly, while testicular histomorphology was affected at high doses in this study, fertility effects in females were not correlated with any obvious organ toxicity.

Parental and early-postnatal exposure to DEHP in rodents also affects the reproductive development of progeny, particularly males. At high doses, overt structural malformations of the tail, brain, urinary tract, vertebral column and sternum are observed. A LOAEL for developmental toxicity in male progeny is established at 5 mg/kg bw/d, based on increased testes weight in a study of prepuberal rats exposed during gestation and lactation. The NOAEL for this effect is 1.2 mg/kg bw/d. In female

## NICNAS Draft Report for Public Comment

progeny in the same study, a LOAEL for developmental toxicity is established at 15 mg/kg bw/d, based on a significant delay in vaginal opening. The NOAEL was 5 mg/kg bw/d.

In a three-generational dietary study in rats, a LOAEL of 14 mg/kg bw/d is established for male developmental toxicity based on decreased testes weight and seminiferous tubule atrophy in F1 and F2 generations. The NOAEL in this study is 4.8 mg/kg bw/d. At higher doses, decreased in utero survival, reduced AGD, undescended testes, retained nipples/areolae, incomplete preputial separation and disruption of spermatogenesis were also observed in F1 and F2 generations.

Biochemical studies in rodents reveal association of DEHP exposure with alterations in Leydig cell steroidogenesis, serum levels of testosterone and luteinizing hormone (LH), and expression of genes crucial for development of the male reproductive system. A LOAEL of 10 mg/kg bw/d is established based on increased serum LH and testosterone levels in rats exposed to DEHP for 28 days during PND 21-48. The NOAEL for these biochemical alterations is 1 mg/kg bw/d.

Overall, rodent studies suggest that the type and severity of reproductive effects from DEHP exposures depend on the time and duration of dosing, and also the age at which effects are monitored. Generally, younger animals are more sensitive than older animals.

Lifetime dietary exposures to DEHP were associated also with dose-dependent increases in the incidence of Leydig cell tumours in some rat studies. However, overall, data are insufficient to determine an association between DEHP exposures and testicular neoplasms.

In humans, studies of potential effects of DEHP on fertility and development are limited and generally based on examining correlations between urinary metabolite levels and reproductive parameters. Overall, available studies do not identify significant, consistent associations between DEHP exposures and reproductive parameters either in adults or children.

Consistent observations of reproductive effects of DEHP in rodents together with data on mode of action suggesting effects on steroidogenesis and expression of genes critical for reproductive system development common to both rodents and humans, suggest that the reproductive toxic effects of DEHP seen in rodents are relevant for humans. Overall, studies support a NOAEL for fertility and developmental effects of DEHP in the dose range of 1–10 mg/kg bw/d. These data are therefore considered for the risk assessment of DEHP in humans.

### Public exposure and health risk

In this assessment, public health risks from DEHP exposure were assessed using a Margin of Exposure (MOE) approach for two exposure scenarios:

- a) use of toys and childcare articles by children, and
- b) use of cosmetic products by the general population.

For children, two routes of exposure to DEHP were considered - dermal exposure during normal handling of toys and childcare articles and oral exposure during intentional or inadvertent mouthing, sucking and chewing of these products, due to leaching of DEHP from the plastic. The rates of leaching of DEHP are based on overseas in vivo and in vitro studies conducted with PVC containing the similar phthalate DINP. The migration rates from plastic articles determined for DINP are considered applicable to toys and childcare articles containing DEHP.

Overseas mouthing studies indicated that children's mouthing behaviour, and therefore the potential for oral exposure, is maximal, reaching up to 3hr/day, in the period between 6 and 12 months of age. Based on these data, for children aged 6-12 months, a reasonable worst-case exposure scenario considered a maximal mouthing time of 3 h/d and a typical exposure scenario considered a mean daily mouthing time of 0.8 h/day.

## NICNAS Draft Report for Public Comment

Given the low acute toxicity, low skin and eye irritation and the absence of skin sensitising potential for DEHP, the risk of adverse acute effects for children arising from handling toys is low.

Health risks for children were estimated for both renal and reproductive effects potentially associated with repeated combined handling and mouthing of toys containing DEHP. Assessments of MOE comparing the DEHP dose at which no adverse reproductive effects were observed in experimental systems and estimated internal DEHP doses for children, derived a MOE for typical conditions of toy use of 157. The MOE for the worst case toy use was 20. Given that MOEs below 100 indicate a risk for a particular adverse effect, the MOE derived for children in this assessment indicates a concern, especially for those children for whom toy use pattern and total contact with toys may be higher than typical, given the sensitivity of developing reproductive organs during the first few months after birth.

Risk estimates for renal effects for the typical and worst case scenarios of toy use by children derive MOEs of 950 and 120, respectively. These MOEs above 100 indicate a low risk of renal effects in children.

The main route of exposure to DEHP from use of cosmetics is through dermal contact. Inhalation exposure is also possible from products applied as aerosols. Current information does not indicate use of phthalates in products most prone to accidental oral ingestion such as toothpastes, mouthwashes, lipsticks and lip-glosses. In the absence of Australian specific data, a worst case exposure scenario for combined cosmetics use was derived based on European use patterns of cosmetics.

Given the low acute toxicity of DEHP, the risk of acute adverse effects for consumers exposed to DEHP through cosmetics is low. However, similar to the risk assessment for children, the potential risks from DEHP from cosmetic use relate to renal and reproductive effects. Estimation of margins of exposure (MOE) comparing the DEHP dose at which no adverse reproductive effects were observed in experimental systems and estimated internal DEHP doses in individuals using cosmetics containing DEHP, derived a MOE for worst case cosmetics use scenario of 26.6. For renal effects, the MOE for the worst case scenario was 441. The low MOE for reproductive effects indicates a concern for the general population and high concern for the subpopulations most at risk for reproductive developmental effects in their progeny i.e. pregnant and breastfeeding women.

# Recommendations

This section provides the recommendations arising from the assessment of DEHP. Recommendations are directed at the appropriate regulatory bodies with responsibilities for regulating chemicals in products and articles. Implicit in these recommendations is that best practice is implemented to minimise public exposure.

## **Recommendation 1 to the Australian Competition and Consumer Commission (ACCC)**

It is recommended that the Australian Competition and Consumer Commission (ACCC) consider appropriate regulatory measures to limit exposure to DEHP resulting from the use of DEHP in toys and childcare articles where significant mouth contact may occur.

*Recommendation 1 is based on the following findings of the PEC assessment:*

- Worst case estimates of the MOE for use of DEHP in children's toys and childcare articles indicate that the risk of reproductive toxicity in children from the use of these products containing DEHP is unacceptable.
- Oral exposure to DEHP through mouthing of toys and childcare articles is the major route of exposure to DEHP
- Reproductive developmental toxicity in children is a serious long term health effect
- Currently there are no restrictions in Australia on the use of DEHP in consumer products including children's toys and childcare articles and there is a potential for introduction and subsequent exposure of children to DEHP via these products.

## **Recommendation 2 to the National Drugs and Poisons Schedule Committee (NDPSC)**

It is recommended that the National Drugs and Poisons Scheduling Committee (NDPSC) consider scheduling the cosmetic use of DEHP in Appendix C of the SUSDP to limit the potential exposure of the public to DEHP from use in cosmetics.

*Recommendation 2 is based on the following findings of the PEC assessment:*

- Estimates of the margin of exposure (MOE) for use of DEHP in cosmetics indicate that the risk of reproductive toxicity for the general population from the use of cosmetics containing DEHP is unacceptable.
- Reproductive toxicity is a serious long term health effect.
- Currently there are no restrictions in Australia on the use of DEHP in cosmetics and there is a potential for introduction and widespread use of cosmetic products containing DEHP.