Australian Government
Department of Health and Ageing
NICNAS

Diethyl Phthalate

Priority Existing Chemical
Draft Assessment Report

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Overview

Background and scope of the assessment

Diethyl phthalate (DEP) (CAS No 84-66-2) was one of nine phthalates declared as a Priority Existing Chemical (PEC) for public health risk assessment for use in toys, child care articles and cosmetics 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 DEP as solvents and plasticisers in industrial and consumer products
- consumer products being potentially significant sources of repeated and long-term exposure of the public to DEP through their use in cosmetic and personal care products and toys
- concerns regarding potential adverse health effects, particularly reproductive and developmental effects, from DEP exposure
- current overseas activities including reassessment and review of the use of phthalates including DEP in certain consumer products.

The purpose and scope of this PEC assessment is to determine the health risks to adults and children from the use of DEP in consumer products such as cosmetics, toys and child care articles, particularly after repeated or prolonged exposure.

Manufacture and importation

Data collected through calls for information specific to the assessment of DEP suggest that the total volume of DEP imported annually to Australia for industrial uses is in the range of 100-300 tonnes. The amount of DEP reported for applications with the potential for public exposure such as toys, child care articles and cosmetics was not more than 100 tonnes per annum for 2005 and 2006. With regard to cosmetic application, DEP is imported as a raw material or mixtures for local formulation and in finished (ready-to-use) products at a ratio of 60:40. Manufacture of DEP as a raw material in Australia was not reported.

Uses

The information collected by NICNAS indicated that in Australia DEP is used mainly in epoxy resins, cosmetics, personal care products and perfumes, with a small proportion in children's toys. It can be used as an alcohol denaturant.

The information also suggests that for cosmetic uses, DEP is imported either as cosmetic ingredients or in fragrance bases for use in the formulation of perfumes, household detergents and personal care products. Concentrations of DEP in these products are varied and range from 0.00004% to 34%. The information on the use of DEP in children's toys and child care articles in Australia is limited. However, DEP as a low molecular weight (LMW) phthalate has been reported to be used in conjunction with other phthalates (as a secondary plasticiser or contaminant), including diethylhexyl phthalate (DEHP) or diisononyl phthalate (DINP).

International sources report that DEP is used as a plasticiser in a diverse range of consumer products and applications such as tools, automotive parts, toothbrushes and toys and as a solvent in cosmetics, fragrances and skin care preparations.

Health effects

DEP is rapidly and almost completely absorbed following oral or inhalation exposure. Bioavailability of 100% is assumed for these routes. In contrast, bioavailability via dermal absorption is not likely to exceed 10%. Tissue distribution of DEP is widespread including foetal tissues but there is no evidence of accumulation. DEP is also rapidly metabolised and excreted, predominantly via the urine with monoethyl phthalate (MEP) as the main metabolite.

DEP has low acute toxicity via all routes and low skin and eye irritation potential. There are case reports of sensitisation to perfumes and plastic articles in patients with dermatitis and other skin diseases although DEP is not considered a skin sensitiser.

Repeated exposure to DEP in rodents caused increased liver and stomach weights in a 16-week dietary exposure study. A weak association between liver toxicity and peroxisome proliferation has been reported for DEP in some studies, but the mechanism for digestive organ enlargement is not confirmed in the critical 16-week study. On this basis, these effects could not be excluded from consideration and therefore are relevant to humans for this risk assessment. A conservative NOAEL of 0.2% in the diet (corresponding to 150 mg/kg bw/d) was established based on dose-dependent increased relative liver weight in females and increased stomach weight in males at 1% in the diet (LOAEL of 750-770 mg/kg bw/d).

Available data do not support a genotoxic or carcinogenic potential for DEP.

The low molecular weight phthalate DEP appears not to be a potent testicular toxin in animal studies. Evaluations of potential DEP toxicity to the developing male rat reproductive system have consistently found no effect on testis weight or testis morphology at doses up to 1016 mg/kg bw/d. However, reduced testosterone production and altered Leydig cell ultrastructure following DEP exposure have been reported. In a critical well-conducted two-generation study, reduced testosterone levels were observed in F0 male rats at a dose of 197 mg/kg bw/d. In addition, there was a slight but statistically significant dose-related increase in the frequency of abnormal and tailless sperms in the F0 and F1 generations, although there was no effect on fertility. Based on this study, a NOAEL of 40 mg/kg bw/d was established.

There was no evidence of foetal or neonatal toxicity after perinatal exposure to DEP at oral doses up to 3200 mg/kg bw/d. None of the effects observed with transitional phthalates (C4-6 backbone), such as epididymal malformations or absence of the epididymis, increased incidence of cryptorchidism, hypospadias, decreased anogenital distance (AGD), delayed preputial separation, and retained areolas/nipples were noted. However, decreased pup weight at weaning and developmental delay (delayed onset of vaginal opening and pinna detachment) were reported in high dose rats in the critical two-generation study. The NOAEL for developmental effects was 197 mg/kg bw/d. The NOAEL for maternal liver and kidney effects was 197 mg/kg bw/d.

In other prenatal exposure studies at 3200 or 5600 mg/kg bw/d, an increased frequency of skeletal variations such as rudimentary cervical and/or lumbar ribs was reported, although these effects generally occurred at or above maternally toxic doses. The increase in supernumerary ribs (either cervical or lumbar) is one of the common anomalies seen in developmental toxicity studies in rodents. In view of the lack of conclusive evidence to assign the skeletal defects to maternal toxicity, these skeletal variations in rodents were interpreted as indicative of slight developmental effects.

There is also some equivocal epidemiological evidence for an association between urinary MEP and the impairment of some reproductive and developmental markers (sperm concentration, motility and morphology, DNA strand breaks in sperm, male reproductive hormones, testicular

function, and AGD) in the human male, but the results remain controversial due to limitations of the study design.

Overall, although the available epidemiological studies do not provide sufficient evidence for a causal relationship between exposure to DEP (measured as urinary MEP) and possible health effects, elements of a plausible mode of action for the effects of DEP on the developing male reproductive system (e.g. reduced testosterone and sperm levels and sperm quality) are considered likely to be parallel in rats and humans if the exposure level of DEP is high enough and within a critical window of development. Therefore the effects on reproductive parameters and development in rats are regarded as relevant to humans for risk characterisation.

Public exposure and health risk

Public health risks from DEP exposure were assessed using a margin of exposure (MOE) approach for two exposure scenarios:

a) use of toys and child care articles by children, and

b) use of cosmetic products by the general population.

For exposure scenario (a), two routes of exposure of children to DEP were considered: dermal exposure during normal handling of toys and child care articles and oral exposure during mouthing, sucking and chewing of these products. The rate of phthalates leaching and migration from articles appears largely determined by the magnitude of the mechanical force applied to an article and the properties of the polyvinyl chloride (PVC) grade comprising the article, and less so by the physicochemical characteristics or concentration of the particular phthalate. Therefore, the migration rates determined under chewing condition for diisononyl phthalate (DINP)–the phthalate most frequently found in toy samples, were used to extrapolate to a mixture of phthalate plasticisers which include DEP. The use of DEP as a secondary plasticiser was considered the most likely scenario. Substitution of DEHP or DINP by DEP as a primary plasticiser was not considered likely. Estimates of DEP content as a secondary plasticiser in toys and child care articles are based on the usage and concentration of dibutyl phthalate (DBP)–an alternative secondary plasticiser reported in use in children's toys in Australia.

Studies conducted overseas indicated that children's mouthing behaviour, and therefore the potential for oral exposure, is maximal in the period between 6 and 12 months of age. Based on these studies, 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/d.

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

Health risks for children were estimated for both systemic toxicity and reproductive/ developmental effects, both of which are potentially associated with repeated handling and mouthing of toys containing DEP. The MOEs were derived by comparing the dose at which no adverse effects were observed in experimental systems (the NOAEL) with the estimated internal DEP doses for children. In both cases, the MOEs were above 10 000 for both the worst-case and typical exposure scenarios of toy use by children. Therefore, the risk of DEP-induced adverse effects from the use of toys and child care articles by children is considered negligible.

For exposure scenario (b), the main route of exposure to DEP from use of cosmetics in the general population 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 of daily use of combined cosmetic products was derived based on European use patterns of cosmetics.

Given the low acute toxicity, low irritation and sensitising potential for DEP, the risk of adverse acute effects for consumers exposed to DEP through cosmetics is very low.

Health risks for the general population were estimated for both systemic toxicity and reproductive/developmental effects, both of which are potentially associated with the repeated use of cosmetic products containing DEP, especially of leave-on products. The MOE derived for general systemic toxicity was greater than 500 indicating low concern in the general population from daily use of combined cosmetic products containing DEP. The MOE for reproductive effects for the general population in the reasonable worst-case scenario was 140, which indicates an adequate safety margin.

As a subset of exposure scenario (b), the health risk to children (12 months or under) was estimated from use of personal care products containing DEP applied over large areas of the body. Based on the estimates for use of body lotions or moisturisers containing 0.25% DEP (the maximum level reported in Australia), the MOE derived for reproductive toxicity was 400 (average), which indicates an adequate safety margin.

The only area of potential concern identified for both adult and children's use of cosmetics was in relation to the use of body lotions or moisturisers. For adults, 0.5% concentration of DEP in body lotions would reduce the MOE for reproductive toxicity in the reasonable worst-case scenario from 140 to 118 which is still an adequate safety margin. For children, 0.5% concentration of DEP in body lotions would reduce the MOE for reproductive toxicity from 400 to 200, which is an adequate, albeit reduced, safety margin.

Overall, the risk estimates for general systemic toxicity indicate low concern for both children and the general population from use of cosmetic products containing DEP at the current reported levels. The risk estimates for reproductive/developmental toxicity also indicate low concern even though the MOEs were lower for these endpoints. A note of caution was identified in relation to the use of one type of cosmetic products used in infants or young children, namely, body lotions or moisturisers, where an increase in the DEP content above 0.5% could reduce the safety margin to unacceptable levels.

The effect of cumulative exposures can arise from use of cosmetics containing multiple phthalates acting on the same biological targets, from the effects of other components in a mixed phthalate used in toys and child care articles, and from the combined exposure scenarios or multiple sources. While cumulative exposures to DEP from multiple sources are addressed under Secondary Notification, the determination of risk from cumulative exposures to multiple phthalates will take into account any risk mitigation measures recommended in each PEC assessment. Risks from cumulative exposure to DEP and DEHP for the two scenarios considered in this assessment is not likely to be higher than that for DEP alone as risk management measures have been implemented for use of DEHP in toys and cosmetics. Risks from cumulative exposure to DEP and other phthalates will be considered on completion of the other phthalate PEC assessments, and if required, further risk mitigation measures recommended.

Recommendations

This section provides recommendations arising from the assessment of DEP. The recommendation is directed at the appropriate regulatory body with responsibilities for regulating chemicals in consumer products. Implicit in this recommendation is that best practice is implemented to minimise public exposure.

Recommendation 1 - to the Advisory Committee on Chemicals Scheduling (ACCS)

It is recommended that the Delegate for Chemicals Scheduling consider listing DEP in body lotion preparations at greater than 0.5% in Appendix C of the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) to limit the potential exposure of the public, particularly young children to high concentrations of DEP from use in these cosmetics.

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

- There is widespread use of body moisturisers in infants or young children who are considered sensitive to the DEP-induced reproductive toxicity.
- Reproductive toxicity induced by DEP may have serious long-term health effects if the exposure to DEP is high and within a critical window of development.
- A cautious approach to the potential risks associated with DEP is warranted, given the level of uncertainty regarding both health effects and the levels of exposure for different population groups.
- The MOE calculation indicates that the use of 0.5% or less of DEP in body lotions would be protective for the public, particularly young children.