Priority Existing Chemical
Draft Assessment Report

Australian Government
Department of Health and Ageing
NICNAS

Diisononyl Phthalate

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DRAFT

Any requests for variation must be made with respect to the draft report and accompanied by a completed application form (NICNAS Form 4a).

Form 4a is available from www.nicnas.gov.au/Forms/Existing_Chemicals/Form4a_PDF.pdf or from the address below.

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NATIONAL INDUSTRIAL CHEMICALS NOTIFICATION AND ASSESSMENT SCHEME

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Overview

Background and scope of the assessment

Diisononyl phthalate (DINP) (CAS No. 68515-48-0 and 28553-12-0) was one of the 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 DINP as plasticisers in industrial and consumer products
- consumer products being potentially significant sources of repeated and long-term exposure of the public to DINP through migration and leaching from products
- concerns regarding potential adverse health effects, particularly reproductive and developmental effects, from DINP exposure
- current restrictions (interim or permanent) overseas for the use of phthalates including DINP 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 DINP 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 DINP suggest that the total volume of DINP imported for industrial uses was in the range of 1000 - 9999 tonnes in 2002 and approximately 600 tonnes in 2004. DINP is imported as a raw material or mixtures for local formulation and in finished (ready-to-use) products. Manufacture of DINP as a raw material in Australia was not reported.

Uses

The information collected by NICNAS indicated that in Australia DINP is used mainly as a plasticiser (plastic softener) for polyvinyl chloride (PVC) products but also in other polymers for adhesives, laminations, resins, surfactants and screen printing inks, with a small proportion in children's toys. DINP is present in imported PVC toys at a concentration range of 0.005 to 35%.

International sources report that DINP is used as a plasticiser for PVC applications, such as in the manufacture of toys and construction materials. DINP is also used in non-PVC applications, such as rubbers, paints, sealants, lacquer and lubricants.

The information on the use of DINP provided by Australian industry did not include any indication that it is used in cosmetic and personal care products. Furthermore, the available information on the use of DINP in cosmetics overseas indicates that it is not used. There is also no information that supports the substitutability of high molecular weight phthalates, such as DINP, for low and mid molecular weight phthalates commonly used in cosmetics.

Therefore, risk characterisation for adults using cosmetics containing DINP is not discussed in this report.

Restrictions (either interim or permanent) have been implemented in EU, USA and Canada on the use of DINP in toys and child care articles that can be placed in the mouth by children. There are currently no restrictions on the use of DINP in toys and child care articles in Australia.

Health effects

Orally administered DINP is rapidly absorbed based on animal and human data. The oral bioavailability of DINP is considered to be 100% for both adults and children. In contrast,

bioavailability via dermal absorption is expected to be not greater than 4%. The available data suggest that dermal absorption of DINP through human skin may be significantly less than that of rat skin. Tissue distribution of DINP is widespread but there is no evidence of accumulation.

DINP is rapidly metabolised to the monoester MINP, which is further oxidatively metabolised to form additional metabolites (mainly carboxy-MINP, hydroxy-MINP and oxo-MINP), or hydrolysed to phthalic acid. These metabolites are rapidly excreted, mostly in urine.

DINP has low acute toxicity via oral, dermal and inhalation routes of exposure and is a slight skin and eye irritant. DINP shows minimal skin sensitisation potential.

DINP is not mutagenic in in vitro bacterial, mammalian or cytogenetic mutation assays and is not clastogenic in an in vivo bone marrow assay.

Incidences of MCL, kidney and liver neoplasia were observed in in vivo rodent carcinogenicity studies. These effects are regarded to be species specific and not relevant to humans.

The main target organs in several species following repeated oral exposure to DINP were the liver and kidney. In rats, liver and kidney toxicity were manifested as increased liver and kidney weights, biochemical changes in enzymes of hepatic origin and histopathological findings. These effects did not appear directly related to peroxisome proliferation. In rabbits following repeated dermal exposures, slight or moderate erythema and desquamation were observed at high doses (2500 mg/kg). No systemic effects were reported.

Overall, a NOAEL of 88 mg/kg bw/d was determined for liver and kidney effects.

DINP has no effects on mating, fertility, fecundity, gestational length or index in rat studies. However, reduced testis weights (without histopathological changes) from 742 mg/kg bw/d and epididymis weights from 2600 mg/kg bw/d DINP were reported in repeated dose studies in mice but not in rats. In rats, DINP was shown to reduce testicular testosterone content and/or production (ex vivo) by male foetuses (GD 21) after gavage exposure during GD 7-21 (at 750 mg/kg bw/d) and GD 14-18 (at ≥ 500 mg/kg bw/d) in a similar pattern as observed with DEHP. Foetal expression of genes involved in androgen synthesis was also reduced at ≥ 1000 mg/kg bw/d. In another study in rats, there were no testosterone production decreases in male foetuses (GD 19) at 750 mg/kg bw/d after GD 13-17 exposure although changes in gene expression levels were seen.

Decreased foetal testicular testosterone content and increased testicular and epididymal agenesis/atrophy in GD 21 male foetuses were also noted in rats exposed to DINP (≥ 600 mg/kg bw/d) from GD 7 to PND 17. Histopathological changes such as degeneration of meiotic spermatocytes and Sertoli cells and agenesis/atrophy of testes and epididymides were also reported at ≥ 1000 and ≥ 600 mg/kg bw/d, respectively. DINP caused nipple retention at doses of ≥ 600 mg/kg bw/d and decreased AGD and/or AGI at ≥ 900 mg/kg bw/d in male offspring. DINP at ≥ 900 mg/kg bw/d also affected spatial learning and increased masculinisation of behaviour in female offspring. An overall NOAEL for fertility-related (or sexual developmental) effects was determined to be 300 mg/kg bw/d based on the collective study results and weight of evidence evaluation.

Changes in pup weight were observed in both sexes, in both one and two generations of rats exposed to DINP and at a much lower dose of approximately 100 mg/kg bw/d. In addition, there was no overt maternal toxicity at this dose level where reduced pup weights were observed. The pup weight reduction was also sustained after birth and continued to PND 21. Taking all together, the reduced pup weight is considered the most sensitive DINP-related adverse effects on offspring growth and development, and hence for the purposes of this review, the developmental NOAEL is established as 31 mg/kg bw/d based on reduced pup weights at 100 mg/kg bw/d and above.

Overall, although the available human data are limited and do not provide sufficient evidence for a causal relationship between exposure to DINP and possible adverse health effects, elements of a plausible mode of action for the effects of DINP on the male reproductive system, offspring growth and sexual differentiation are considered parallel in rats and humans if the exposure to DINP is high and within a critical window of development. Therefore, the effects observed in animal studies are regarded as relevant to humans for risk characterisation.

Public exposure and health risk

Public health risks from DINP exposure were assessed using a margin of exposure (MOE) approach for use of toys and child care articles by children. As it was found that there is no evidence of use of DINP in cosmetics in Australia or overseas, risk characterisation was not carried out for the general population using cosmetics containing DINP.

For the toy and child care articles exposure scenario, two routes of exposure of children to DINP were considered: dermal exposure during normal handling of toys and child care articles and oral exposure during mouthing, sucking and chewing of these products. Migration rates were determined under chewing condition for DINP in overseas in vivo and in vitro studies.

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

Health risks for children were estimated for both systemic (liver and kidney) toxicity and reproductive/developmental effects, both of which are potentially associated with repeated handling and mouthing of toys containing DINP. The risk estimates for systemic (liver and kidney) toxicity for the typical and worst case scenarios of toy use by children give MOEs of 2895 and 365, respectively. The MOE for reproductive and developmental effects for the typical scenario was 9868 and 1020, respectively and for the worst case scenario, 1243 and 128, respectively. In the three cases, the MOEs were above 100 for both the worst-case and typical exposure scenarios of toy use by children. Therefore, an adequate safety margin exists for DINP-induced adverse effects from the use of toys and child care articles by children.

Overall, the risk estimates for systemic toxicity, and reproductive and developmental effects indicate low concern for children at the current reported levels of DINP in toys and child care article.

The effect of cumulative exposures to phthalates can arise 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 the risks of cumulative exposures to DINP 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 of children to DINP in toys and child care articles with or without DEHP at maximum 1%, together with co-exposure to another phthalate, DEP in cosmetics at maximum 0.5% in body lotions are considered low as cumulative MOEs for the three critical health effects identified are all, albeit marginally, above 100. Risks from cumulative exposure to DINP and other phthalates will be considered on completion of other phthalate PEC assessments, and if required, further risk mitigation measures recommended.

Conclusion

The current PEC assessment has evaluated the human health risk from the uses of DINP in children's toys and child care articles. Current risk estimates do not indicate a health concern from exposure of children to DINP in toys and child care articles even at the highest (reasonable worst-case) exposure scenario considered.

The risks from cumulative exposure of children to DINP in toys and child care articles with or without DEHP at maximum 1% together with co-exposure to DEP in cosmetics at maximum 0.5% in body lotions have been considered and found to be acceptable based on current public health risk management measures.

No additional recommendations to the existing controls in place for the public health risk management for the use of DINP in toys and child care articles are required based on the findings of this assessment.

Secondary Notification

Under Section 64 of the *Industrial Chemicals (Notification and Assessment) Act 1989*, the secondary notification of a chemical that has been assessed under the Act may be required where change of any circumstances that may warrant a reassessment of its hazards and risks occurs.

In the case of DINP, specific circumstances include the following:

- additional information becoming available on the adverse health effects of DINP;
- DINP being used in cosmetic products;
- additional sources of public exposure to DINP other than toys and child care articles and cosmetics being identified; and
- additional information or events that change the assumptions for estimating the cumulative risk in this assessment.

The Director of NICNAS must be notified within 28 days of the introducer becoming aware of the above or other circumstances prescribed under Section 64(2) of the Act. It is an offence under section 64 of the Act if the Director is not notified of the specified circumstances of which the introducer has become aware.