Australian Government

Department of Health and Ageing
Office of Chemical Safety and
Environmental Health

Ms Andrea Kunca
Office of Medical Devices
Therapeutic Goods Administration

Dear Ms Andrea

Re: Diethylhexyl phthalate in medical devices.

I write to inform you about an Advisory Committee on Chemicals Scheduling (ACCS) recommendation regarding diethylhexyl phthalate (DEHP) in medical devices.

In December 2010 the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) submitted a scheduling application to the delegate of the Secretary to the Department of Health and Ageing (the delegate) requesting that use of DEHP in cosmetic products be banned. DEHP was declared as a Priority Existing Chemical in March 2006 by NICNAS for public health risk assessment. The decision for the declaration was based on DEHP's toxicology profile, including the potential for adverse health effects (particularly reproductive effects) from its exposure.

As the delegate, I considered the proposal and decided that ACCS advice was required. The ACCS considered the scheduling of DEHP at its first meeting held in February 2011. An extract of the ratified minutes of the meeting, contained in the delegate's June 2011 final reasons for DEHP, is attached for your information. Please note that any sections highlighted in yellow contain information which was not released publicly, and as such should be treated confidentially.

The ACCS was concerned that DEHP in medical devices was a human toxicity issue that should be brought to the TGA's attention. DEHP is used in certain medical devices, such as colostomy bags, where patients could be exposed to significant concentrations of DEHP. Furthermore, as these medical devices have to be attached to patients for 24 hours a day over a life span, this continual exposure and potential uptake of DEHP may require further investigations.

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If you have any queries in relation to this matter please contact the Medicines and Chemicals Scheduling Secretariat on (02) 6289 1359 or e-mail to smp@health.gov.au

Yours sincerely

Dr Brian Priestly
Delegate of the Secretary to the Department of Health and Ageing

21 December 2011

Encl: Extracts of the Ratified Minutes of the ACCS Meeting – Diethylhexyl phthalate.

1.3 DIETHYLHEXYL PHTHALATE

DELEGATE'S REFERRAL TO EXPERT ADVISORY COMMITTEE

The delegate considered the scheduling of diethylhexyl phthalate and decided to seek advice from the ACCS on the following:

Diethylhexyl phthalate (DEHP) – proposal to schedule DEHP, including consideration of:

- a parent entry in Schedule 6 or 7;
- prohibition of cosmetic use through listing in Appendix C.

The delegate also decided to seek advice on potential cut-offs and exemptions, including possibly restricting the use in toys and childcare articles to less than 0.05 per cent.

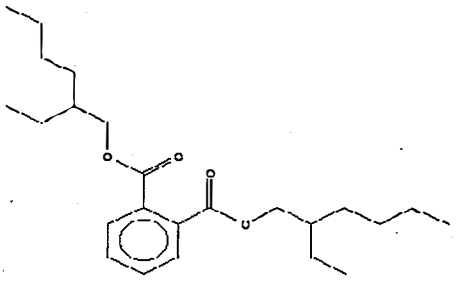
EXPERT ADVISORY COMMITTEE RECOMMENDATION

The Committee recommended that the use of DEHP in cosmetic products be prohibited by inclusion in Appendix C. The Committee also recommended an implementation period of six months after the delegate's final decision.

The Committee additionally recommended that the delegate advise TGA of the need to review concerns from the potential leaching of DEHP when used in some medical devices.

BACKGROUND

DEHP is a benzenedicarboxylic acid ester of phthalic acid (a chemical class commonly referred to as phthalates). The CAS and IUPAC name for DEHP is bis(2-ethylhexyl) phthalate and the chemical structure is:



DEHP is one of the most extensively used phthalates worldwide. In the USA, approximately 97 per cent of DEHP is used as a plasticiser in polyvinyl chloride (PVC). In the European Union (EU), DEHP use represents around half of the total volume of phthalates used as plasticisers.

In Australia DEHP, and DEHP containing PVC, is used in flooring, waterproofing

materials, cable sheathing/insulation, PVC labels, surface repair resin moulds, epoxy and polyurethane products, rubber components in automotive brake assemblies and hot melt adhesives for automotive assembly and repair. DEHP is also used in fragrance bases for perfumery and cosmetic products. DEHP is additionally used as a plasticiser in medical devices such as blood bags and dialysis equipment.

DEHP was declared a Priority Existing Chemical (PEC) for public health risk assessment under the *Industrial Chemicals (Notification and Assessment) Act 1998* in March 2006. The decision for declaration was based on:

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

The National Industrial Chemicals Notification and Assessment Scheme (NICNAS) PEC Review on DEHP included a scheduling recommendation. This review was therefore referred by NICNAS to the delegate for consideration. The delegate agreed that this was a matter for scheduling consideration and that advice from the ACCS was needed.

SCHEDULING STATUS

Not currently scheduled. Dimethylphthalate in sunscreens or personal insect repellents for human use (except in preparations containing 0.5 per cent or less of dimethylphthalate) is currently listed in Appendix C, but appears sufficiently different in structure from DEHP as to not capture DEHP as a derivative.

INITIAL SUBMISSIONS

Applicant's Submission – NICNAS's Priority Existing Chemical Assessment Report

The NICNAS PEC report found that, based on the toxicity profile of DEHP, it would be appropriate to prohibit cosmetics containing this substance, and requested that DEHP be listed in Appendix C to limit the potential exposure of the public to DEHP from use in cosmetics. This recommendation was based on:

- The estimate of the margin of exposure (MOE) for use of DEHP in cosmetics indicated that the risk of reproductive toxicity for the general population was unacceptable. Reproductive toxicity was a serious long term health effect.

- At this time there were no restrictions in Australia on the use of DEHP in cosmetics and there was a potential for the introduction and widespread use of cosmetic products containing DEHP.
- The PEC report indicated that use of DEHP in cosmetic products (in the EU) and personal care products (in California) had been prohibited. In September 2009, Canada added DEHP to its List of Prohibited and Restricted Cosmetic Ingredients.
- The PEC report further indicated that there were no regulatory restrictions on the use of DEPH in cosmetics in Asia and other non-EU countries. This raised the possibility of importing DEHP containing cosmetics manufactured in these countries.

The PEC report also 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. This recommendation was 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 indicated that the risk of reproductive toxicity in children from the use of these products containing DEHP was unacceptable.
- Oral exposure to DEHP through mouthing of toys and childcare articles was the major route of exposure to DEHP. Reproductive developmental toxicity in children was a serious long term health effect.
- There were no restrictions in Australia on the use of DEHP in consumer products including children's toys and childcare articles and there was a potential for introduction and subsequent exposure of children to DEHP via these products.
- The NICNAS's referral letter to the delegate indicated that the ACCC had already declared certain products containing DEHP unsafe under the *Trade Practices Act 1974* (in January 2011 this Act was renamed as the *Competition and Consumer Act 2010*). Members noted that in March 2010, the ACCC enforced an interim ban (effective until 2 September 2011) restricting the supply of certain children's plastic products, including toys, childcare articles, and eating vessels and utensils that contain, or have a component that contains, more than 1 per cent by weight DEHP. The ban applied to those products that could readily be sucked and/or chewed and were intended to be use by children up to and including 36 months of age.
- DEHP was not included in the Australian/New Zealand Standard AS/NS ISO 8124 *Safety of Toys* and prior to the ACCC action there were no restrictions on the use of DEHP in consumer products, including toys.
- The EU and the USA have restricted the use of DEHP to less than 0.1 per cent (by weight) of the plastic used in any type of toys and childcare articles and Canada was in the process of implementing a similar restriction.

Toxicology

Members noted the following toxicology summary for DEHP from the PEC Report:

Absorption, distribution, metabolism and excretion.	
Rate and extent of oral absorption.	Completely and rapidly absorbed from the gastrointestinal tract. Most of the administered DEHP was systematically absorbed and excreted in urine. Bioavailability in both children and adults was estimated to be 100%.
Dermal absorption.	*In vivo* experiments conducted on rats and guinea pigs show that 9% and 26% of the applied DEPH was absorbed respectively. Human skin was less permeable (4-fold) to DEHP than rat skin therefore the bioavailability of DEHP in humans was not likely to be exceed 5%.
Distribution.	Liver, kidney, testes and blood were the main distribution sites. The injected DEHP rapidly distributed but there was no evidence of accumulation.
Metabolism.	DEHP is rapidly hydrolysed by lipases to monoethylhexyl phthalate and 2-ethylhexanol. Lipases are found in all tissues, especially in the pancreas, therefore rapidly metabolise in the intestine.
Elimination and excretion.	Orally administered DEHP was excreted mainly as metabolites with small amount of the parent compound. In rats and mice elimination was rapid with 85-95% excreted in the first 24 hours and in humans 75% was excreted within 2 days.

Acute toxicity		
Study	**Species**	**Result**
Oral	Rat	LD_{50} > 20000 to > 40000 mg/kg bw.
Oral	Mouse	LD_{50} > 9860 mg/kg bw
Dermal	Rabbit	LD_{50} = 24750 mg/kg bw
Inhalational (4 hours)	Rat	LC_{50} > 10.62 mg/L
Intravenous	Rat	LD_{50} =200 mg/kg bw
Skin and eye irritation	Rabbit	Minimal irritant
Skin sensitisation	Guinea pig	Non-sensitiser.

Genotoxicity	Non-genotoxic

Carcinogenicity	Increased incidences of hepatocellular adenomas and carcinomas were observed in mice. The LOAEL for tumour induction in male mice was 292 mg/kg bw/d. The NOAEL was 98 mg/kg bw/d.
Reproductive toxicity	Higher doses resulted in decreased male reproductive organs, including testes and prostate, weights, decreased sperm motility, sperm concentrations and complete infertility. A NOAEL for effects on fertility in mice was 14 mg/kg bw/d and LOAEL was 140 mg/kg bw/d.

Developmental toxicity	DEHP induced overt structural malformations (mainly tail, brain, urinary tract, gonads vertebral column and sternum) in rats. More subtle effects, such as anogenital distance (AGD) was also recorded in several other studies. Based on reduced AGD, a LOAEL of 113 mg/kg bw/d was determined in rats.

Neurotoxicity and delayed neurotoxicity	Not determined.

- In animals, DEHP exhibited low acute oral, dermal and inhalation toxicity. Intravenous and intraperitoneal administration of DEHP resulted in higher acute toxicity than oral or dermal administration; however, the acute toxicity via these

routes was still low. Members also noted that such exposures were very limited. Therefore, DEHP was expected to have low acute toxicity in humans.

- DEHP induced minimal skin and eye irritation in animals and did not induce skin irritation in human volunteers. Data were insufficient to determine the respiratory irritation potential of DEHP. In animal studies, DEHP was not a skin sensitiser and limited data indicated no sensitisation reactions in humans. Human studies indicated correlations between the risk of bronchial obstruction and plasticiser-emitting components of the indoor environment. However, there was insufficient evidence supporting a causal relationship between respiratory effects and DEHP.
- The repeated dose toxicity of DEHP was evaluated in a number of animal species, in both short-term (few weeks) and life-time studies by several routes of exposure. The most pronounced effects were on the liver (hepatomegaly, peroxisome proliferation), kidney (increased organ weights, mineralisation of renal papilla, tubule cell pigmentation and chronic progressive nephropathy) and testes (atrophy, vacuolated Sertoli cells, multinucleated gonocytes, Leydig cell hyperplasia).
- Exposure to DEHP during gestation and sensitive age post-natal periods in rodents also caused significant effects on reproductive parameters and development.
- Liver effects were reported in several rodent species. In a dietary study in rats fed with DEHP (at dose levels up to 939 mg/kg bw/d), hepatotoxicity was indicated by significant increases in serum albumin, absolute and/or relative liver weights and peroxisome proliferation at 146.6 mg/kg bw/d and above. The NOAEL for these effects was 28.9 mg/kg bw/d. A similar NOAEL, 25 mg/kg bw/d, was established based on hepatic changes after sub-chronic intravenous exposure in rats. The liver effects induced by oral administration of DEHP in rodents were not reported in oral administration studies with marmoset monkeys.
- DEHP-associated toxicity was consistently observed in kidneys of rats and mice. A LOAEL for these effects was established at 146.6 mg/kg bw/d from a 104-week rat dietary study, based on increased absolute and relative kidney weights. Mineralization of renal papilla, tubule cell pigmentation and chronic progressive nephropathy were observed at higher doses. The NOAEL for kidney effects was 28.9 mg/kg bw/d. No information related to kidney toxicity was available in monkeys. Human studies on DEHP-induced toxicity to kidneys were not available. The mechanism of DEHP-related toxicity to kidneys was not clear but it appeared that it was not related to peroxisome proliferation as kidneys lesions were found in both PPARα-null and wild-type mice. Given the lack of information on DEHP-induced kidney toxicity in primates (including humans), the relevance to humans of kidney effects observed in rats could not be excluded.
- Testicular toxicity of DEHP in repeated dose studies in rats manifested as decreased testes weights and testicular atrophy, increased bilateral aspermatogenesis, immature or abnormal sperm forms, seminiferous tubular degeneration, Sertoli cell vacuolation or complete loss of spermatogenesis. In a 13-week rat dietary study, a LOAEL of 37.6 mg/kg bw/d was established based on an increased incidence of Sertoli cell

vacuolation. Significantly decreased absolute and relative testicular weights, mild to moderate seminiferous tubule atrophy and Sertoli cell vacuolation were observed at higher doses. The NOAEL was 3.7 mg/kg bw/d.

- The consistent finding of testicular effects in rats and mice was in contrast to evidence from studies in marmosets where no significant treatment-related changes in testicular histology or more gross parameters were observed from oral exposures to DEHP at doses up to 2500 mg/kg bw/d. However the number of studies were limited and may not cover critical windows for testicular toxicity especially in young and developing animals.
- Therefore, although there were no reports of DEHP-induced testicular toxicity in primates, the relevance to humans of the effects observed in rats could not be excluded based on the plausible mode of action.
- DEHP was tested in a variety of short-term genotoxicity assays with predominantly negative results. Overall, DEHP was regarded as non-genotoxic.
- Carcinogenicity studies in rodents indicated significant dose related increases in hepatocellular and Leydig cell tumours. The LOAEL for tumour induction (hepatocellular neoplasms and mononuclear cell leukaemia [MCL]) in male rats was 147 mg/kg bw/d. The NOAEL was 28.9 mg/kg bw/d in males. The evaluator asserted that the mechanism by which DEHP and other peroxisome proliferation induce hepatotoxicity and hepatocarcinogenicity in rodents were regarded as not relevant to humans. Similarly, MCL was well known to occur spontaneously with high incidence in F344 rat strains and rare in other rat strains. This neoplasm was not found in other mammalian species and had no histological comparable tumour type in humans. Therefore the evaluator has asserted that DEHP induced MCL observed in rats was not considered relevant to humans.
- In a lifelong exposure study, DEHP was administered in the diet at 30, 95 and 300 mg/kg bw/d to male rats. At the highest dose increased incidences of hepatocellular adenomas and carcinomas were observered. Similarly, the incidence of benign Leydig cell tumours in the highest dose group was 28 per cent; almost twice the incidence in the control group (16 per cent). The NOAEL for both liver and testicular carcinogenic effects was determined to be 95 mg/kg bw/d. The evaluator indicated that given the similarities in regulatory pathways within the hypothalamic-pituitary-thyroid (HPT) axis of rats and humans, the chemicals which induced Leydig cell tumours in rats by disrupting regulatory mechanisms within the HPT axis were likely to have similar effects in humans. However, the susceptibility of humans to hyperplasia and tumours may be less than rodents, as human Leydig cells were less sensitive to the proliferative effects of luteinizing hormone.
- In a prenatal developmental toxicity study, 0.025, 0.05, 0.10 and 0.15 per cent DEHP were administered to mice throughout gestation. Reduced maternal body weight gain was noted at 0.10 per cent and above, mainly due to reduced gravid uterine weight. Increased resorptions, late foetal deaths and malformed foetuses, and decreased foetal weight and viable foetuses were observed at 0.10 per cent and above. Increased

malformed foetuses were seen also at 0.05 per cent and above. The external malformations included unilateral and bilateral open eyes, exophthalmia, exencephaly, and short, constricted or no tail. Visceral malformations were localised predominantly in the major arteries. Skeletal defects included fused and branched ribs and misalignment and fused thoracic vertebral centra. The NOAEL for maternal toxicity was 91 mg/kg bw/d (0.05 per cent) and for developmental toxicity was 44 mg/kg bw/d (0.025 per cent).

- In another prenatal developmental toxicity study, DEHP at doses of 40, 200, or 1000 mg/kg bw/d was administered by gavage to pregnant mice (15/group) from gestation day 6 to 15. At gestation day 17, decreased viable pups and increased resorptions and post-implantation loss were observed at 1000 mg/kg bw/d. Cardiovascular abnormalities, tri-lobed left lungs, fused ribs, fused thoracic vertebral centres and arches, immature livers and kidney anomalies were also observed at this dose. At 200 mg/kg bw/d, there was a slight increase in foetuses with intra-muscular or nasal haemorrhage or dilated orbital sinuses. There also were a small number of foetuses with anomalous innominate or azygous blood vessels at this dose level. A NOAEL of 200 mg/kg bw/d was established for maternal toxicity and 40 mg/kg bw/d for developmental toxicity.
- In another postnatal developmental study (rats exposed to DEHP during gestation and lactation), a NOAEL for developmental toxicity was established at 1.2 mg/kg bw/d, based on increased testes weight in prepuberal rats at 5 mg/kg bw/d. These weight increases were not associated with any histopathological or biochemical alterations. In a continuation of the study, a NOAEL for female developmental toxicity was established at 5 mg/kg bw/d, based on a significant delay in vaginal opening observed at 15 mg/kg bw/d in female offspring.

Effects observed in humans

- In humans, a number of studies have been conducted examining correlations between maternal mono(2-ethyl-5-hydroxyhexyl)phthalate (MEHHP) levels and gestation length, onset of puberty and anogenital distance (AGD). Overall, these studies did not provide convincing evidence of developmental effects from DEHP exposure in humans. This was related to the low power of studies due to small sample size, non-representative sample (usually one study centre) and uncertainties about the significance of the measured endpoints, for example AGD, as an indicator of developmental toxicity in humans.
- In a case report, three preterm infants artificially ventilated through PVC respiratory tubes developed unusual lung disorders resembling hyaline membrane disease during the fourth week of life. One infant died two weeks after birth, the other two were healthy at follow-up 20 months later. DEPH was detected in the lung after autopsy of the infant who died. The estimated inhalation exposure in the three infants ranged between 1 μg/h to 4,200 μg/h based on the concentrations of DEHP in the condensate collected from the water traps of the respirator tubing. However, this was likely to be an over-estimate as infants were not exposed to the condensate. DEHP, but not monoethylhexyl phthalate (MEHP), could be detected in urine samples.

- A mortality study carried out on 221 workers in a German plant producing DEHP reported eight deaths (including one carcinoma of the pancreas and one bladder papilloma). These workers had been exposed to DEHP for three months to 24 yr (average 11.5 yr). No information about exposure levels were provided; however, in two other reports by the same group, exposure levels in the plant ranged from 0.01 mg/m^3 to 0.16 mg/m^3.
- Occupational exposure to PVC and other products in the plastics industry was assessed in a case-control study of testicular cancer using self-administered questionnaires (148 cases and 315 controls). An increased risk of testicular cancer was observed (as evaluated by an increased odds ratio (OR) of 6.6; 95 per cent confidence interval: 1.4 - 32) for exposure to DEHP plasticised PVC, but not for other types of plastics. It was assumed that a potential oestrogenic effect of the chemicals used as plasticizers for PVC may have resulted in increased risk of testicular cancer. The evaluator, however, asserted that considering the design of the study (self administered questionnaires and occupational exposure to a number of different chemicals used in association with PVC plastics), no link could be established between testicular cancer and DEHP. This study was followed up by a larger case-control study taken from the Swedish Cancer Registry during 1993 - 1997. A total of 791 matched pairs completed a questionnaire regarding exposure. Overall exposure to PVC plastics gave an OR of 1.35 (confidence interval = 1.06 - 1.71). No dose-response relationships were found. There was no clear association between testicular cancer and exposure to PVC.
- Another study measured DEHP and MEHP concentrations in the plasma and peritoneal fluid of 35 women identified by laparoscopy as having endometriosis. There was no difference in the proportion of surgical patients compared to control women with detectable DEHP or MEHP (91.4 per cent compared to 92.6 per cent respectively). There was a significant difference in the median concentration of DEHP in the patients compared to control women (0.57 μg/mL compared with a control value of 0.18 μg/mL) but no difference in median MEHP concentration.
- In another study of endometriosis, plasma phthalate levels in 85 infertile women with endometriosis were compared with levels in 135 age-matched fertile control women undergoing laparoscopic sterilisation in the same hospital. Mean plasma DEHP levels in women with endometriosis were at least 3 times higher than levels in the controls. Differences were statistically significant.
- In a gonadotrophins study the gonadotropins and gonadal hormone levels of 74 male workers exposed to elevated levels of di-n-butyl phthalate (DBP) and DEHP in a PVC factory were measured. Urinary monobutyl phthalate (MBP) and MEHP levels (normalised to creatine) were significantly higher in exposed workers compared with 63 controls (MBP 644.3 μg/g versus 129.6 μg/g; MEHP 565.7 μg/g versus 5.7 μg/g). Circulating testosterone was significantly lower in exposed workers (8.4 μg/g) versus control workers (9.7 μg/g) and was negatively correlated with MBP and MEHP.

- In a reproductive toxicity study, blood phthalate levels in 41 premature thelarche patients (beginning of breast development without other sexual development signs) and 35 controls were compared. There was a statistically significant difference in average blood DEHP levels. DEHP was detected in 25 of the samples from premature thelarche patients at a mean concentration of 450 μg/L (187 - 2098 μg/L), MEHP concentration ranged from 6.3 to 38 μg/L. DEHP was detected in 5 of 35 blood samples from control patients at a mean concentration of 70 μg/L (276–719 μg/L). The reported levels in the control group were unusually high compared with the background MEHP concentration in urine in the normal population (mean 4.27, range 3.80–4.79 μg/L) and may reflect patient exposure to medical procedures within the hospital. A Member noted that this comparison may be invalid, unless the blood/urine relationship was known.
- In another reproductive toxicity study, cord blood samples were collected from 84 consecutive newborns (including a set of twins) delivered at an Italian hospital. DEHP and/or MEHP were detected in 74 of 84 cord blood samples with a mean (range) DEHP cord blood serum concentrations of 1.19 (0–4.71) μg/mL and MEHP of 0.52 (0-2.94 μg/mL). Mean gestational age, but no other parameter, was significantly lower in MEHP-positive neonates (38.16 weeks) versus MEHP-negative neonates (39.35 weeks). However, the levels measured in blood were unusually high compared to other studies.

Observed effects in humans – Evaluator's conclusion

- The evaluator concluded that a number of human reproductive toxicity studies have attempted to link maternal MEHP levels with gestation length, onset of puberty and AGD. These studies, however, did not show effects of DEHP exposure on developmental parameters.

Toys and child care articles – Exposure and Risk

The PEC report identified that the two dominant routes of exposure to DEHP through the use of plastic toys and childcare articles were:

- dermal exposure during normal handling of toys and childcare articles. Absorption via the dermal route, however, was significantly low; and
- oral exposure during intentional or inadvertent chewing, sucking and biting of these products. The PEC report estimated that a six-month old infant would absorb 27.8 μg/kg bw/day of DEHP at typical exposure conditions and 231 μg/kg bw/day at worst-case exposure conditions. This was based on studies which demonstrated that 6 month old infants were within an age range showing maximum mouthing behaviour, and have the lowest body weight in this age range.

Risk estimates take into account the likelihood for renal and reproductive effects at future life stages related to long term exposure through repeated handling and mouthing of toys. The MOE estimated from the internal DEHP dose in children and the dose at which no adverse effects were observed on the kidneys or the reproductive systems in animal systems was:

Toxicity	NOAEL mg/kg bw/d	MOE for typical scenario exposure	MOE for worst case scenario exposure
Reproductive	4.8	157	20
Kidney	28.9	950	120

The reproductive NOAEL used for this estimate came from a three-generational dietary study with rats for male developmental toxicity.

The risk estimates for kidney toxicity, in both scenarios of toy use by children derived MOEs above 100 and hence indicateed low risk of adverse effects on kidneys. The risk characterisation for DEHP exposure of children from use of toys and childcare articles indicated that under typical conditions of toy use the MOE for children for reproductive toxicity was marginally above 100. However, the MOE for the worst case scenario was significantly less than 100 indicating a risk of adverse effects in this scenario.

NICNAS sought to manage this risk by recommending to ACCC that it consider appropriate regulatory measures to limit exposure to DEHP resulting from the use of DEHP toys and child care articles.

Cosmetics – Exposure and Risk

The main route of exposure to DEHP from use of cosmetics was through dermal contact. Inhalation exposure was also possible from products applied as aerosols. Oral exposure was considered negligible as available information did not indicate use of phthalates in products most prone to accidental ingestion, such as toothpastes, mouthwashes, lipsticks and lip-glosses. The potential risks from cosmetic use were related to long term exposure through repeated use, especially of leave-on products, such as nail polish and face cream.

The evaluator indicated that due to lack of sufficient data on the cosmetic use pattern, conservative plausible assumptions had been used to determine the risks to consumers.

The potential risks from cosmetic use were related to long term exposure through repeated use, especially of leave-on products. The internal dose of DEHP from daily use of various DEHP-containing cosmetic products was estimated to be 154.7 μg/kg bw/d considering a "worst-case" scenario of daily use of all (leave-on, wash-off and spray application) cosmetic products. Additional assumptions were as follows:

- DEHP content in cosmetics was similar to that reported for DEP (diethyl phthalate) in a limited number of cosmetic products in Australia.
- Bioavailability of DEHP via the dermal route was 5 per cent and via the inhalation route was 100 per cent.

Calculated MOE for critical health effects of DEHP from estimated aggregate exposure to cosmetic products for the general population were:

Type of toxicity	NOAEL	MOE for reasonable worst

reached when multiple lipophilic drugs were pre-mixed in intravenous fluid bags and agitated for 1 h.

Hazard Classification

Undiluted DEHP, for occupational purposes, was classified as a reproductive toxicant Category 2 requiring the Risk phrases R60: *May impair fertility* and R61: *May cause harm to the unborn child* in the Australian Hazardous Substances Information System (HSIS) of Safe Work Australia. These risk phrases apply to products containing more than 0.5 per cent DEHP.

February 2011 Pre-meeting Submissions

ACCC

The submission advised that an interim ACCC ban on children's plastic products with more than 1 per cent DEHP came into effect on 2 March 2010. The submission further indicated that the interim ban would become a permanent ACCC ban, expected by March 2011.

The submission asserted that the delegate's proposed limit of 0.05 per cent DEHP in respect to toys and childcare articles was inconsistent with the ACCC's ban on such goods containing more than 1 per cent DEHP. It was asserted that restricting the use in toys and childcare articles to less than 0.05 per cent DEHP would raise significant compliance issues with suppliers, and cause safety concerns amongst consumers regarding these products. The submission asserted that the ACCC's restriction on DEHP reflects industry concern regarding the ban.

NICNAS

NICNAS, in addition to refering the DEHP PEC report, also made a pre-meeting submission. This mainly reiterated the PEC report and ACCC's pre-meeting submission.

The submission asserted that determination of the level of exposure to DEHP from cosmetics high risk subpopulations was difficult. The results of the large biomonitoring studies show that female adults had maximum exposure levels. This raised concerns that the high exposure scenarios with MOEs extremely close to or below 100 may be applicable to the subpopulation most at risk for reproductive developmental effects in their progeny i.e. pregnant and breastfeeding women. Similarly, for young children undergoing critical developmental processes there was concern regarding reproductive developmental toxicity from potential DEHP exposure through use of lotions and creams.

Reiterated that risks arising from uses other than in cosmetics and toys and childcare articles were not considered in the NICNAS PEC Report. The submission noted that the undiluted form of DEHP met the Schedule 7 criteria, based on "a severe hazard from repeated and unprotected use or a significant risk of producing irreversible toxicity,

	mg/kg bw/d	case exposure scenario
Reproductive	4.8	31
Kidney	28.9	187

The estimated margin of exposure (MOE) for reasonable worst case exposure scenario for reproductive toxicity was less than 100 in children and marginally above 100 for the general population. The evaluator therefore indicated that the risk of reproductive toxicity from simultaneous use of multiple cosmetic products containing DEHP for children and the general population was high.

The risk estimate for chronic effects to kidneys derived a MOE above of 187 indicating low concern for kidney toxicity in the general population using multiple cosmetic products containing DEHP.

Exposure to DEHP from use of personal care products was also estimated specifically for children. Based on these estimates MOE for reproductive effects of DEHP exposure was found to be below and marginally above 100. The calculated MOE for reproductive effects of DEHP for children was:

Infant Age	$Dose_{int.derm}$ (μg/kg bw/day)	MOE
Newborn	61.7	77
6 months	48.2	99
12 months	42.9	105

NICNAS therefore recommended banning DEHP for cosmetic use through Appendix C. No suggestion was made regarding any potential for a low concentration cut-off.

Other uses – Exposure and Risk

Members noted that industry use of DEHP was widespread, including as a plasticiser for PVC and polymers for coatings. Plasticised containers for cosmetic and personal care products may represent a source of exposure to phthalates, including DEHP, through leaching of plasticiser from the container into the product. The evaluator, however, stated that currently there were no data available regarding this issue.

DEHP leaching from PVC storage bags and tubing for medical use indicated that PVC used in medical devices contains a relatively high proportion (20 to 40 per cent) of plasticiser. The mean levels of DEHP reported in blood or blood products stored in DEHP containing PVC bags ranged from 0 μg/mL to 650 μg/mL, depending on storage conditions, duration of storage and blood product stored. The highest content of 650 μg/mL was detected in platelet concentrate supernatant stored in PVC bag for 42 d at 4°C. The DEHP content extracted from drug formulations stored in plasticised PVC ranged from 0.2 μg/mL to 54.64 μg/mL, varying significantly depending on the contact area, temperature and storage conditions. The highest DEHP concentrations were

which may involve serious acute or chronic health risks or even death if it is inhaled, taken internally or penetrates the skin". The submission further noted, however, that the impact of listing DEHP in Schedule 7 for uses other than cosmetics may require further consultation.

EXPERT ADVISORY COMMITTEE DISCUSSION

Members generally agreed that relevant matters under Section 52E(1) included (a) risks and benefits; (b) the purpose and extent of use; and (c) toxicity of a substance.

Members discussed whether there was merit in prohibiting the use of DEHP in cosmetics. Members agreed that although DEHP's acute toxicity was low, significant concerns existed with regard to reproductive toxicity, should exposure occur. It was generally agreed that the PEC report's approach in establishing MOEs below 100 for exposure through cosmetic use was sufficiently concerning as to warrant consideration of a prohibition through scheduling. Another Member noted that there were a number of international precedents for such an action. Members agreed that an Appendix C entry for cosmetic use of DEHP was appropriate.

Members then considered whether there should be a low concentration cut-off from the Appendix C entry to allow for unintended contamination. Members noted advice that there had been a few cross-contamination incidences involving small amounts of DEHP inadvertently leaching into cosmetic products during the manufacturing process. These incidences were usually reported from multi-product manufacturing plants. Members agreed, however, that this was a good manufacturing practices issue rather that a matter needing to be addressed through scheduling. In addition, a Member was concerned that setting an Appendix C cut-off would in turn imply that deliberate use up to that cut-off was acceptable, contradicting the Committee's intent that DEHP should not be an ingredient in cosmetics at any level. Members agreed that there was insufficient information at this time to allow the setting of a low concentration cut-off from the Appendix C entry for cosmetic use of DEHP.

Members, noting the intent of the ACCC's ban for use of DEHP in certain children's products to become a permanent ban, also considered whether a similar restriction needed to be implemented through scheduling. Members generally agreed that regulation of these types of products was normally best done through the ACCC's mechanisms. It was also noted that most toy manufacturers, given the nature of their business, would tend to be more aware of the ACCC controls. In addition, the ACCC had better recall powers should breeches occur. Members agreed that it was not appropriate to duplicate the ACCC controls through scheduling.

Some Members additionally raised concern as to whether the ACCC's ban was sufficiently protective, as the EU had imposed a more than 0.1 per cent ban (versus the

ACCC's 1 per cent cut-off). A Member was also concerned that, as the EU's cut-off was significantly lower than that for Australia, it was possible that toy manufactures in countries without DEHP controls could see Australia as a "dumping ground" for those products they were not able to export to the EU. Members noted advice from NICNAS that the reason for the ACCC's 1 per cent cut-off was based on conservative scenario calculations which indicated that this level of DEHP would result in a MOE of 860, a significant safety margin in protecting the health and safety of children. It was noted that the EU cut-off may in fact be too conservative. Members generally maintained, therefore, that ACCC remained the appropriate authority for considering this aspect of controls for DEHP. It was agreed that concerns arising from the difference between the ACCC's and overseas cut-offs for DEHP in children's products was a matter for ACCC to consider and resolve.

Members then discussed whether there was a need to create a parent entry for DEHP. Members noted that while the hazard from undiluted DEHP may be indicative of a Schedule 7 entry, the question was whether there was an actual risk necessitating such scheduling action, particularly given the wide spread use and potential for regulatory impact of such a move. In this regard a Member was particularly concerned about the lack of submissions from the affected industries. The Member stated that it was possible that these industries were not aware that scheduling could impose controls on articles containing scheduled poisons.

Members noted that, according to the PEC, exposure to DEHP in articles required a mechanical force to release the DEHP (i.e. children chewing on toys). Members therefore agreed that any leaching risk from products, other than those already identified by ACCC, would be very low. Members also noted that it currently appeared that undiluted DEHP only had industrial uses. It was noted that Safe Work Australia listed DEHP in its Australian Hazardous Substances Information System and Members agreed that it appeared reasonable, on the current available data, that the consequent Occupational Health and Safety controls on workers handling DEHP were sufficiently protective as to not warrant additional measures through scheduling. The Members agreed that a parent entry was not necessary based on current use patterns of DEHP.

A Member raised some concerns regarding medical use of DEHP, such as colostomy bags, where patients could be exposed to significant concentrations (up to 40 per cent) of DEHP. The Member indicated that these bags have to be attached to patients for 24 hours a day over a life span and this continual exposure and potential uptake of DEHP was concerning. Another Member noted that such exposure, if any, would depend on the type of colostomy bag, as many are attached in such a way that would minimise dermal contact. Members agreed that DEHP, when used in medical devices, was a TGA regulatory issue rather than a scheduling matter. It was noted that TGA, in consultation with other international agencies, had already commenced investigations regarding DEHP in medical devices. Members agreed, however, that it was still appropriate to recommend that the delegate advise TGA of the need to review concerns from the potential leaching of DEHP when used in some medical devices.

Implementation date

Members discussed whether there was a need to allow additional time for the cosmetic industries to respond to the prohibition of DEHP from their products. A Member asserted that this was a significant change and that affected industries may need to reformulate. Other Members noted that the Committee had considered the risk from exposure to DEHP via cosmetic use to be serious enough to warrant an Appendix C entry, so it followed that this risk was also serious enough to require implementation without additional delay. The Committee agreed that an implementation timeframe of six months appeared appropriate.

DELEGATE'S DISCUSSION

The delegate concluded that the recommendations of the ACCS were clear and appropriately supported. The delegate also agreed that an implementation period of six months was appropriate.

The delegate also noted that the NICNAS published information regarding its controls on cosmetics clearly advised that a cosmetic included personal care / toiletry preparations i.e. a substance or preparation intended for placement in contact with any external part of the human body with a view to altering the odours of the body; or changing its appearance; or cleansing it; or maintaining it in good condition; or perfuming it; or protecting it.

The delegate agreed that the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989* included (a) risks and benefits (b) the purpose and extent of use and (c) toxicity of a substance.

DELEGATE'S INTERIM DECISION

The delegate decided to include use of diethylhexyl phthalate in cosmetic products in Appendix C.

SUBMISSIONS ON INTERIM DECISION

No submissions were received on the interim decision.

DELEGATE'S FINAL DECISION

The delegate confirmed that use of diethylhexyl phthalate in cosmetic products be included in Appendix C. The delegate also confirmed an implementation date of 1 January 2012.

APPENDIX C – New Entry

DIETHYLHEXYL PHTHALATE for cosmetic use.