C4-6 side chain transitional phthalates: Human health tier II assessment

21 April 2016

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,2-Benzenedicarboxylic acid, dicyclohexyl ester	84-61-7
1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	84-69-5
1,2-Benzenedicarboxylic acid, dibutyl ester	84-74-2
1,2-Benzenedicarboxylic acid, dihexyl ester	84-75-3
1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester	85-68-7
1,2-Benzenedicarboxylic acid, bis(2-methoxyethyl) ester	117-82-8
1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters	68515-42-4
1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7 rich	71888-89-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic

data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The Phthalate Esters Panel of the American Chemistry Council (ACC) derived three categories of phthalates based on use, physicochemical and toxicological properties. Low molecular weight (LMW) phthalates are defined as those produced from alcohols with carbon side-chain lengths of <= C3. High molecular weight (HMW) phthalates are those produced from alcohols with straight or ring-structured carbon chain lengths of >= C7. Transitional phthalates were defined as those produced from alcohols with straight or branched carbon chain lengths of C4–6. In addition, if the level of C4–6 constituents exceeds 10 %, regardless of the total carbon number in the ester side-chain, it is suggested that the chemical be placed in C4–6 transitional category (ACC, 2006 revised).

On the basis of the ester side-chain length, the chemicals assessed in this report belong to the C4–6 transitional phthalate category. The chemical BBP (CAS No. 85-68-7) is an asymmetric diester, consisting of one linear (butyl C4) and one ring-structured (benzyl C5) ester side-chain. The ester side-chain length of DMEP (CAS No. 117-82-8; containing an oxygen atom) is considered equivalent to that of DBP (CAS No. 84-74-2); and DcHP (CAS No. 84-61-7; containing a ring structure) is between those of BBP and DnHP (CAS No. 84-75-3). The chemical DiHepP (CAS No. 71888-89-6) consists of C4–6 (methyl hexyl isomers) at 80 %, and thus its linear backbone is predominantly C6 (ACC, 2006). The chemical D711P (CAS No. 68515-42-4), based on its description, is expected to include constituents with a chain length of six or less, although composition information is not available. Given that D711P is prohibited in cosmetic products (CosIng Regulation Annex II), and is being a subject to authorisation under the European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) (see **International restrictions** section), similarly to other members of this group, it is considered suitable for inclusion in this group assessment.

For toxicological endpoints where the data are incomplete or unavailable, information from structurally similar chemicals is used to examine the potential toxicity. The hazard findings from the Priority Existing Chemical (PEC) assessments of diethylhexyl phthalate (DEHP; CAS No. 117-81-7), DBP, DMEP and BBP (NICNAS, 2010; 2013; 2014; 2015) will be considered for read-across (filling data gaps) for other members of the group.

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information (NICNAS, 2008).

The chemical DBP has reported cosmetic use in fragrance bases for cosmetic and personal care products, and in nail polish.

The chemical DBP has reported domestic use in fragrance bases for household products.

Members of the group have reported commercial uses including:

- BBP as a plasticiser for polyvinyl chloride (PVC) consumer products including gumboots, toys (secondary plasticiser), play and exercise balls, in adhesives, textile printing inks, automotive refinish, road-marking paints, light industrial, wood coatings and building products;
- DBP as a plasticiser for rubber and PVC consumer products including children's toys (secondary plasticiser), play and exercise balls, in adhesives, sealants, coatings, paints, nitrocellulose lacquers, and textile printing inks;
- DiBP as a plasticiser for rubber and PVC, and in adhesives;
- DMEP as a plasticiser for PVC consumer products including imported toys (secondary plasticiser), inflatable water products, hoppers, and play and exercise balls;
- DcHP in adhesives and printing inks; and
- DiHepP as a specialist PVC plasticiser and in printing inks.

The chemicals (except DnHP and D711P) have reported site-limited uses including:

- as plasticisers for manufacture of PVC and polymer-related applications;

- as solvents for diluting organics; and
- in catalysts for polypropylene and fibreglass manufacture (DiBP).

While these uses of the chemicals are commercial and targeted at professional users or site-limited, the articles and the paints produced in factories in Australia and elsewhere have domestic uses, and the chemicals can, over time, leach out into the environment during use. This may result in some exposure by the general community. An Australian company indicated that BBP will be phased out in end-use home products, e.g. furniture finishes.

From the mandatory call for information on phthalates in 2004 and followed by a voluntary call in 2006, BBP, DBP and DMEP were identified in actual or potential use in cosmetics, children's toys and childcare articles in Australia, while these uses are not reported for the remaining members of this group. NICNAS received no report on uses of DnHP and D711P from the calls for information in 1999, 2004 and 2006.

International

The chemicals (except BBP and DBP) have no reported cosmetic use and are not listed in the:

- Personal Care Products Council's International Nomenclature Cosmetic Ingredient (INCI) dictionary; or
- Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011).

The following international uses have been identified through REACH dossiers; Galleria Chemica; Substances in Preparations in Nordic countries (SPIN) database; European Commission (EC) Cosmetic Ingredients and Substances (CosIng) database; INCI dictionary; US National Library of Medicine Household Products database; and eChemPortal.

Members of the group have reported cosmetic uses including:

- BBP in nail polish and enamels;
- DBP in foundation and other makeup (excluding eye makeup), manicuring preparations, nail creams and lotions, nail polish and enamels, and personal cleansing products.

Members of the group have reported domestic uses including:

- BBP in arts and crafts, auto products, home maintenance products, landscape and yard pastes;
- DBP in auto products (aerosol) and home maintenance products;
- DcHP: auto products (liquid); and
- DiHepP: home maintenance products.

The chemicals have reported commercial uses including in:

- rubber and plastic products including fillers, construction materials, insulation materials, machinery and transport equipment, building interiors, vinyl floors and walls, vehicle interiors, electrical batteries and accumulators, and toys; and
- non-polymer applications such as adhesives, sealants, lubricants, coatings, paints, lacquers, varnishes, printing inks, textile finishes, and in the paper and pulp industry.

The chemicals have reported site-limited uses including in:

- plasticisers for manufacturing PVC and polymer-related applications;
- solvents for diluting organic peroxides; and
- intermediates for manufacture and formulation.

Restrictions

Australian

The chemicals DBP, DiBP, and DMEP (together with DEHP) are currently listed in Schedule 10/Appendix C of the Poisons Standard (*Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)*) to limit the potential exposure of the public, including young children, from their actual or possible use in cosmetics, based on the PEC and IMAP assessment findings and recommendations (NICNAS, 2013; 2014; NICNAS IMAP Tranche 9, 2014).

A similar exclusion of BBP for cosmetic use will be a subject for consideration by the Scheduling Delegate in early 2016, based on the NICNAS PEC recommendation (NICNAS, 2015).

International

Members of the group are listed in the:

- EC Cosmetics Regulation Annex II (List of substances prohibited in cosmetic products; CosIng): BBP, DBP, DMEP and D711P.

- REACH Regulation Annex XIV (Authorisation List of substances of very high concern (SVHC)): BBP, DBP and DiBP (together with DEHP).
- REACH Regulation Annex XVII (Restriction List): BBP and DBP 'shall not be used as substances or in mixtures, in concentrations greater than 0.1 % by weight of the plasticised material, in toys and childcare articles. Such toys and childcare articles containing these phthalates in a concentration greater than 0.1 % by weight of the plasticised material shall not be placed on the market.'

The chemicals are also candidates for further restrictions as they are listed in the:

- EC Article 15 (List of substances classified as carcinogenic, mutagenic, or toxic for reproduction (CMR) (CosIng): DiBP and DiHepP. These chemicals 'must not be intentionally added to cosmetic products (SCCP, 2005).
- Candidate List for authorisation under REACH: DMEP, DcHP, DnHP, DiHepP and D711P.
- US Environmental Protection Agency's Phthalates Action Plan (US EPA, 2012a revised), which is an initiative to address the manufacturing, processing, distribution in commerce, and/or use of eight phthalates, including BBP, DBP and DiBP.
- US EPA's Universe of Chemicals list for potential endocrine disruptor screening and testing (US EPA, 2012b): BBP, DBP, DiBP, DMEP, DcHP, DnHP, and D711P.
- Environment Canada's Categorisation Results of Domestic Substances List (DSL) as high priority for further work: DMEP and D711P.

Existing Worker Health and Safety Controls

Hazard Classification

Members of the group are classified as hazardous, with the following risk phrases, for human health in the Hazardous Substances Information System (HSIS, Safe Work Australia):

- Reprotoxic Category 2 (R61 'May cause harm to the unborn child') and Reprotoxic Category 3 (R62 'Possible risk of impaired fertility'): BBP, DBP, DiBP, DMEP, D711P.
- Reprotoxic Category 2 (R61): DiHepP.

Exposure Standards

Australian

DBP: TWA (time weighted average) = 5 mg/m^3 (Hazardous Substances Information System (HSIS) (Safe Work Australia).

International

The chemicals have workplace exposure standards (Galleria Chemica):

- DMEP, DiBP, DBP, DcHP, DnHP, DiHepP, D711P (all chemicals):

  STEL (short-term exposure limit) = 5 mg/m^3 (Sweden).

- DiBP: TWA = 3 mg/m^3 (Iceland), 5 mg/m^3 (Ireland; New Zealand);

  LTEL (long-term exposure limit) = 5 mg/m^3 (United Kingdom).

- DBP: TWA = 3 mg/m^3 (Iceland); 5 mg/m^3 (Ireland; Canada; New Zealand);

  LTEL (long-term exposure limit) = 5 mg/m^3 (United Kingdom).

- DcHP: TWA = 3 mg/m^3 (Iceland), 5 mg/m^3 (Ireland; New Zealand);

  LTEL (long-term exposure limit) = 5 mg/m^3 (United Kingdom).

Health Hazard Information

The hazard characterisation for this group is based on a read-across or trend analysis approach. The assessment information is obtained from relevant individual phthalate hazard assessments, the Phthalates Hazard Compendium and PEC assessments for DEHP, DBP, DMEP and BBP (NICNAS, 2008; 2010; 2013; 2014; 2015), and available studies for C4–6 phthalates (BBP, DBP, DiBP and DcHP) registered with ECHA (REACH). It is noted that DcHP, DnHP, DiHepP and D711P are not registered with ECHA at the time of this assessment.

Toxicokinetics

The collective results of available studies for the C4–6 transitional phthalates (NICNAS, 2008; 2010; 2013; 2014; 2015; REACH dossiers) suggest that:

- The chemicals are rapidly and almost completely absorbed following oral exposure. The bioavailability of BBP, DBP and DMEP from oral exposure is assessed as 100 % for both adults and children. Bioavailability from dermal absorption is unlikely to exceed 5 % of the applied dose in humans. Data on inhalation absorption are limited; therefore, a default bioavailability of 100 % is considered appropriate for this group.
- Following absorption, distribution of the chemicals is widespread into tissues; however, there is no evidence of accumulation in the body.
- The chemicals are also rapidly metabolised and excreted in the urine, predominantly as hydrolytic monoesters. Further enzymatic oxidation of the alkyl chain can occur in some of the phthalates, resulting in more hydrophilic oxidative metabolites.

Acute Toxicity

Oral

The chemicals are expected to have low acute oral toxicity. The median lethal doses (LD50s) in rodents are >2000 mg/kg bw and consistent for a number of chemicals (BBP, DBP, DiBP, DMEP, DcHP, DnHP, DiHepP) across the group (NICNAS, 2008, 2013, 2014; 2015; REACH).

Dermal

The chemicals are expected to have low acute dermal toxicity. The median lethal doses (LD50s) in rodents are >2000 mg/kg bw and consistent for a number of chemicals (BBP, DBP, DMEP, DiHepP) across the group (NICNAS, 2008, 2013, 2014; 2015; REACH).

Inhalation

The chemicals are expected to have low acute inhalation toxicity. Rats survived exposures of 3.2 mg/L/1-hour DcHP, 8.9 mg/L/6-hour DMEP, and 15.68 mg/L/4-hour DBP (NICNAS, 2008, 2013, 2014; REACH).

Corrosion / Irritation

Skin Irritation

The available data suggest that the chemicals cause minimal skin irritation based on studies on BBP, DBP, DiBP, DMEP, DcHP, DnHP, and DiHepP (NICNAS, 2008, 2013, 2014; 2015; REACH).

Eye Irritation

The available data suggest that the chemicals cause minimal eye irritation based on studies on BBP, DBP, DiBP, DMEP, DcHP, and DiHepP (NICNAS, 2008, 2013, 2014; 2015; REACH). Heated DBP was an irritant to the eyes (Haz-Map).

Sensitisation

Skin Sensitisation

The available data suggest that the chemicals are not likely to be skin sensitisers in humans. Negative results have been reported for BBP, DBP, DiBP, DMEP, and DiHepP (NICNAS, 2008, 2013, 2014; 2015; REACH).

The chemical DcHP was reported to cause skin sensitisation reactions following topical application to the skin of mice using the standard recognised local lymph node assay (LLNA). However, the stimulation index (SI) values showed no dose-response relationship (2.22, 2.82, 1.94 for doses of 2.5 %, 5 %, and 10 %, respectively) and an effective concentration needed to produce a stimulation index of three (EC3) value could not be determined. Also, the SI at high dose was not statistically significant compared with the threshold of 1.9 for a positive result (REACH). On this basis, DcHP is not considered classifiable as a skin sensitiser according to the approved criteria (NOHSC, 2004).

Observation in humans

Allergic contact dermatitis attributed to DBP has been reported in workers handling epoxy resins (Haz-Map).

The chemicals DiHepP and DEHP, together with another five C6–C13 phthalates, were tested in a 104-person panel, human repeated insult patch test (HRIPT); the results showed no evidence of irritation or sensitisation (Medeiros et al., 1999).

Repeated Dose Toxicity

Oral

The most common systemic target organs observed in repeated dose toxicity studies using the phthalates are the liver and kidney, although the severity of effects and the doses at which effects were seen varied for different phthalates. In addition, for some of the phthalates, liver and kidney effects, when related to peroxisome proliferation or a rodent-specific mode of action, are unlikely to be relevant for a human health risk assessment.

Liver effects (including increased organ weights, often with biochemical and histopathological changes) were seen with all chemicals, such as BBP (381 mg/kg bw/d), DiBP, DBP (752 mg/kg bw/d), DMEP (1000 mg/kg bw/d), DcHP (500 mg/kg bw/d), DnHP (1824 mg/kw bw/d), DiHepP (333 mg/kg bw/d), and D711P. At these dose levels, kidney effects (increased organ weights) were reported with BBP, DBP, DMEP, DiHepP, and D711P only (NICNAS, 2008, 2013, 2014; 2015; CMA, 2000).

Genotoxicity

Based on the weight of evidence and the non-genotoxic profile of phthalates in general, the chemicals are not expected to have mutagenic or genotoxic potential in humans.

The chemicals BBP, DBP and DiHepP were negative in several in vitro tests (bacterial reverse mutation or mammalian cytogenetic mutation assays). The chemicals DiBP, DcHP, and DnHP were negative in bacterial mutation assays and positive in comet assays (NICNAS, 2008, 2013; 2015; Ahbab et al., 2014).

The chemical DMEP was positive in a dominant lethal test in mice; however, this is likely to be related to its teratogenic effects, rather than being attributable to genotoxicity (NICNAS, 2014). The genotoxicity of the analogue DEHP has been reviewed extensively and it is regarded as non-genotoxic (IARC, 2011).

Carcinogenicity

Based on the weight of evidence, the available data do not provide adequate evidence of carcinogenicity for the chemicals in humans.

No adequate long-term carcinogenicity studies are available for the chemicals, except BBP. Given the chemicals are not considered to be genotoxic, they are not likely to be genotoxic carcinogens. Although mononuclear cell leukaemia (MCL) in rats and hepatocellular adenomas/carcinomas in rats or mice were the most common tumour types reported with phthalates in general, they are not regarded as relevant to humans. MCL has not been found in other mammalian species and has no directly comparable manifestations in humans. Liver tumours linked to peroxisome proliferation, which may be disregarded for human risk characterisation, have been assessed for the well-studied phthalates such as DEHP and diisononyl phthalate (DiNP) (NICNAS, 2010; 2012). The results of pancreatic adenomas and bladder carcinomas observed with BBP are considered equivocal (NICNAS, 2015).

For DEHP, testicular (Leydig cell) tumours (as well as liver tumours) were also reported following lifetime exposure in rats. Considering 'the relevance to human cancer of the multiple molecular signals and pathways that lead to cancer elicited by DEHP in several target tissues (e.g. the liver and testis) in rodents, the International Agency for Research on Cancer has classified DEHP as 'possibly carcinogenic to humans' (Group 2B)' (IARC, 2011).

Reproductive and Developmental Toxicity

The C4–6 transitional phthalates have been well characterised for reproductive and developmental toxicity.

The best studied transitional phthalate is DEHP (NICNAS, 2010; NICNAS IMAP Tranche 4, 2013). The chemical DEHP is well characterised for its effects on male reproductive system development, as well as other reproductive and developmental effects. While the phthalates in this group (apart from BBP and DBP) are less studied, most have shown results consistent with those for DEHP.

According to the NICNAS PEC assessments (2013; 2014; 2015), evidence in animal reproductive and developmental toxicity studies consistently shows that BBP, DBP and DMEP adversely affect fertility and offspring development. The mechanism of toxicity involves overt effects on the male rat reproductive system (reduced testis weight, testicular pathology and sperm abnormalities). Reduced pup weight; reduced foetal testosterone content and production; and altered sexual differentiation and development, such as decreased anogenital distance (AGD), delayed preputial (foreskin) separation, and nipple retention, are also observed at low doses of BBP or DBP (as low as 50 mg/kg bw/d) in male rodents. The chemical DMEP shows even more severe and irreversible effects, such as reduced number of pregnancies, implantations and litter sizes, testicular atrophy and embryolethality, probably due to the combined effects of its phthalate monoester and oxidative alcohol metabolites (2-methoxyethanol and methoxyacetic acid).

ECHA's evaluation of DiBP as a substance of high concern (ECHA SVHC support document, 2009) concluded that 'DiBP was found to adversely affect the reproductive organs in adult males in experimental studies which may affect their fertility. The chemical DiBP was also found to be a developmental toxicant.' In addition, DiBP was as potent as DBP and DEHP in reducing foetal testosterone production.

Like BBP, DBP, DiBP and DMEP, D711P is also evaluated as a Reproductive Toxicant Category 1B (or Repr 1B) with the risk phrase H360Df 'May damage the unborn child. Suspected of damaging fertility' (ECHA SVHC support document, 2011a). This is consistent with the current classification of these five chemicals on HSIS (see **Regulatory** section).

The chemical DiHepP is evaluated as Reproductive Toxicant category 1B with the risk phrase H360D 'May damage the unborn child' (ECHA SVHC support document, 2011b). In a two-generation reproductive toxicity study conducted in accordance with standard test guidelines, DiHepP was reported to cause testicular abnormalities, reduced weights of testes and accessory reproductive organs, reduced sperm counts and daily sperm production, reduced AGD, increased time to balanopreputial separation and nipple retention in the 750 mg/kg bw/d group of the first (F1) generation. Fertility was also significantly reduced in this group. In the second (F2) generation offspring, AGD and weight gain during lactation were also significantly decreased in both the 300 and 750 mg/kg bw/d dose groups. Furthermore, in female rats given DiHepP by oral gavage on gestation day (GD) 6–20, there were significant reductions in uterine weight, increased resorptions

and reduced foetal weight at 750 mg/kg bw/d. Foetal examination revealed malformations and variations of both the skeletal system and the viscera including ectopic testes (McKee et al., 2006). Therefore, the available data support the classification of DiHepP as Repr 1B with the same risk phrase (H360Df) as DBP.

Although currently classified as Reproductive Toxicant category 1B, the risk phrase H360FD 'May damage fertility. May damage the unborn child.' has been proposed for DnHP, indicating a higher degree of certainty about its antifertility effects (ECHA SVHC support document, 2013). The chemical DnHP caused dose-related adverse effects on fertility (380–1670 mg/kg bw/d) during a continuous 98-day breeding study in mice. Crossover mating studies demonstrated that reproductive parameters were affected in both males (reduced weights of epididymides and testes, and sperm abnormalities) and females (reduced uterine weight). The chemical DnHP also had teratogenic effects (NICNAS, 2008).

The chemical DcHP is evaluated as being less potent than DnHP with the assigned risk phrase H361 'Suspected of damaging fertility or the unborn child' (REACH). Although DcHP treatment did not result in clear embryolethality and teratogenicity, unlike DnHP, it significantly decreased foetal weight at 750 mg/kg bw/d. Both DcHP and DnHP induced a significant and dose-related decrease in AGD at doses =250 mg/kg bw/d (Saillenfait et al., 2009). Also, in a two-generation reproductive toxicity study, DcHP decreased prostate weight, caused atrophy of testicular seminiferous tubules in male rats, and inhibition of body weight gain in both sexes. The DcHP-induced decreases in AGD and appearance of nipples in male offspring, although less severe, were considered mediated through a similar mechanism as DBP (Hoshino et al., 2005; Yamasaki et al., 2005).

The phthalate mode of action on the male reproductive system (testicular toxicity) and on spermatogenesis has been studied extensively for BBP, DBP and DEHP. There is experimental evidence to support the hypothesis that transitional phthalates produce antiandrogenic effects by inhibiting foetal testosterone production and insl3 (insulin-like factor 3, a foetal Leydig cell product critical for testis descent) (NICNAS, 2010, 2013; 2015). Given the similarity of reproductive effects induced by the transitional phthalates, it is reasonable to assume that the mode of action would be similar between the phthalates of this group and be applicable to humans if the exposure to the phthalates is high and within a critical window of development.

Considering the chemicals of this group have similar hazard classifications (although DcHP was assigned a slightly lower degree of certainty by ECHA) and they have similar reproductive profiles in experimental studies, particularly at high doses, a conservative no observed adverse effect level (NOAEL) of 10 mg/kg bw/d, derived for the testicular toxicity effects of DBP, is used for data gap filling across members of the group.

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is adverse effects on fertility and development (mediated by testicular toxicity, abnormal spermatogenesis, reduced pup weight, and altered sexual differentiation). The chemicals can also cause increased kidney and liver weights with histopathological changes in the liver unrelated to peroxisome proliferation (repeated dose toxicity).

Public Risk Characterisation

The risks of adverse reproductive effects from direct exposure via handling and mouthing toys and childcare articles containing BBP, DBP or DMEP (as secondary plasticisers at the current reported level of <0.5 %) are low (NICNAS, 2013, 2014; 2015).

In cosmetics, risk estimates for DBP (including for combined exposure to multiple phthalates) indicate a concern for the general population and high concern for subpopulations most at risk for reproductive and developmental effects in their progency, e.g. pregnant and breastfeeding women and children. While there is no current indication of BBP, DiBP or DMEP being used in cosmetic or domestic products in Australia or overseas, they might be considered as a possible substitute for other phthalates that are subject to regulation (e.g. DEHP), based on their properties, functions and uses. Possible substitution of BBP, DiBP and DMEP for hazardous phthalates should be prevented by imposing a similar regulatory framework on all of the commonly used phthalates classified as toxic for reproduction, (e.g. BBP, DBP, DiBP, DMEP and DEHP).

The public health risks for the general population (without occupational sources of exposure) from other uses of the chemicals are considered low, based on the evaluation of margins of exposure (MOEs). This approach compares the NOAEL of 10 mg/kg bw/d for reproductive effects with the following intakes for the most widely used phthalate of a relatively high vapour pressure in this group, DBP, deriving MOEs of >100 (i.e. adequate safety margin):

- from biomonitoring value (95th percentile): 24.4 µg/kg bw/d (reviewed by NICNAS, 2013);
- from calculated exposure estimate (95th percentile): 38.6 µg/kg bw/d (Worthmuth et al., 2006).

As the remainder of the group are less commonly used than DBP and are less likely to be found in the high exposure uses of children's toys and cosmetics, the biomonitoring results for DBP are expected to represent the worst-case.

Occupational Risk Characterisation

During product formulation, dermal and inhalational exposure of workers to the chemicals may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintenance of equipment. Worker exposure to the chemicals at lower concentrations may also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical long-term systemic and reproductive effects, the chemicals could pose an unreasonable risk to workers (especially pregnant and breastfeeding women) unless adequate control measures to minimise occupational exposures are implemented.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation** section).

NICNAS Recommendation

Further risk management is required. Sufficient information is available to recommend that risks to public health and safety from the potential use of these chemicals in cosmetics be managed through changes to poisons scheduling, and risks to workplace health and safety be managed through changes to classification and labelling.

Assessment of the chemicals is considered to be sufficient provided that risk management recommendations are implemented and all requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Public Health

The chemical BBP has been recommended for listing in Schedule 10/Appendix C of the SUSMP, based on the NICNAS PEC assessment (NICNAS, 2015).

Work Health and Safety

The chemicals DcHP, DnHP and DiHepP are recommended for classification and labelling for reproductive effects under the current approved criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. There is no change recommended to the classification of BBP, DBP, DiBP, DMEP, and D711P.

This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62) Repro. Cat 2 - May cause harm to the unborn child (T; R61)	May damage the unborn child. Suspected of damaging fertility - Cat. 1B (H360Df)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemicals from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical DBP, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals— Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemicals has not been undertaken as part of this assessment.

References

Ahbab MA, Undeger U, Barlas N, Basaran N. 2014. In utero exposure to dicyclohexyl and di-n-hexyl phthalate possess genotoxic effects on testicular cells of male rats after birth in the comet and TUNEL assays. Human and Experimental Toxicology 33:230-9

American Chemistry Council (ACC) Phthalate Esters Panel. 2006. High Production Volume (HPV) Chemical Challenge Program, Test Plan for the Phthalate Esters Category. Revision to Test Plan dated December 10, 2001. Prepared by ExxonMobil Biomedical Sciences, Inc. Accessed May 2014 at **http://www.epa.gov/hpv/pubs/summaries/benzene/c13467rt3.pdf**

Chemical Manufacturers Association (CMA). 2000. A 21-day feeding study of 711 phthalate to rats: effects on the liver lipids and liver. EPA/OTS, Doc #40+8626201, NTIS/OTS0509543. Accessed June 2014 at **http://chem.sis.nlm.nih.gov/chemidplus/rn/68515-42-4**

CIUCUS (Compilation of Ingredients Used in Cosmetics in the United States. 2011. Washington DC: Personal Care Products Council

CosIng (Cosmetic Ingredients& Substances) Database. European Commission. Available: **http://ec.europa.eu/consumers/cosmetics/cosing/**

eChemPortal. Organisation for Economic Co-operation and Development (OECD). Available: **www.echemportal.org**

Environment Canada. Overview and results of DSL categorization. Available: **http://www.ec.gc.ca/lcpe-cepa/eng/subs_list/DSL/DSLsearch.cfm**

European Chemicals Agency (ECHA). 2009. SVHC support document for identification of diisobutyl phthalate as a substance of very high concern because of its CMR properties. Accessed June 2014 at **http://echa.europa.eu/documents/10162/d418f8b0-ba93-402a-97fd-1e340d22c541**

European Chemicals Agency (ECHA). 2011a. SVHC support document for identification of 1,2-benzenedicarboxylic acid, di-C7-11 branched and linear alkyl esters (DHNUP) as a substance of very high concern because of its CMR properties. Accessed June 2014 at **http://echa.europa.eu/documents/10162/3903d3cb-823b-45fd-bdb0-91fbffd190d6**

European Chemicals Agency (ECHA). 2011b. SVHC support document for identification of 1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich (DIHP) as a substance of very high concern because of its CMR properties. Accessed June 2014 at **http://echa.europa.eu/documents/10162/1c803fe7-2ced-43e7-9411-7cc298310f96**

European Chemicals Agency (ECHA). 2013. SVHC support document for identification of dihexyl phthalate as a substance of very high concern because of its CMR properties. Accessed June 2014 at **http://echa.europa.eu/documents/10162/2b3f9a8d-2dc1-4482-8997-8a1e426d8a53**

European Chemicals Agency (ECHA). Candidate List of Substances of Very High Concern for Authorisation (SVHC). Available: **http://echa.europa.eu/candidate-list-table**

Galleria Chemica. Available: **https://jr.chemwatch.net/galleria/**

Hazardous Substances Information System (HSIS). Safe Work Australia. Available: **http://hsis.safeworkaustralia.gov.au/HazardousSubstance**

Haz-Map. Information on Hazardous Chemicals and Occupational Diseases. US National Library of Medicine. Available: **http://hazmap.nlm.nih.gov/index.php**

Hoshino N, Iwai M, Okazaki Y. 2005. A two-generation reproductive toxicity study of dicyclohexyl phthalate in rats. Journal of Toxicological Sciences. 30:79-96

INCI (International Nomenclature Cosmetic Ingredients) Dictionary. Personal Care Products Council. Available: **http://gov.personalcarecouncil.org/jsp/gov/GovHomePage.jsp**

International Agency for Research on Cancer (IARC). 2011. Some chemicals present in industrial and consumer products, food and drinking-water. IARC monographs on the evaluation of carcinogenic risks to humans, v. 101

McKee RH, Pavkov KL, Trimmer GW, Keller LH, Stump DG. 2006. An assessment of the potential developmental and reproductive toxicity of di-isoheptyl phthalate in rodents. Reproductive Toxicology 21:241-52

Medeiros AM, Devlin DJ, Keller LH. 1999. Evaluation of skin sensitization response of dialkyl (C6-C13) phthalate esters. Contact Dermatitis 41:287-9

National Occupational Health and Safety Commission (NOHSC). 2004. Approved Criteria for Classifying Hazardous Substances, 3rd ed [NOHSC:1008(2004)]. Commonwealth of Australia. Accessed June 2014 at **http://www.safeworkaustralia.gov.au/sites/SWA/about/Publications/Documents/258/ApprovedCriteria_Classifying_Hazardous_Substances_NOHSC1008-2004_PDF.pdf**

NICNAS. 2008. Phthalates Hazard assessment reports and Phthalate Hazard Compendium. Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Available: **http://www.nicnas.gov.au/chemical-information/other-assessment-reports/phthalates-hazard-assessment-reports**

NICNAS. 2010. Priority Existing Chemical (PEC) assessment report no. 32: Diethylhexyl phthalate (DEHP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Available: **http://www.nicnas.gov.au/chemical-information/pec-assessments**

NICNAS. 2013. Priority Existing Chemical (PEC) assessment report no. 36: Dibutyl phthalate (DBP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Available: **http://www.nicnas.gov.au/chemical-information/pec-assessments**

NICNAS. 2014. Priority Existing Chemical (PEC) assessment report no. 38: Di(methoxyethyl) phthalate (DMEP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Available: **http://www.nicnas.gov.au/chemical-information/pec-assessments**

NICNAS. 2015. Priority Existing Chemical (PEC) assessment report no. 40: Butyl benzyl phthalate (BBP). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed November 2015, **http://www.nicnas.gov.au/chemical-information/pec-assessments**

NICNAS. Inventory Multi-tiered Assessment and Prioritisation (IMAP): Human health tier II assessment for 1,2-benzenedicarboxylic acid, bis(2-ethylhexyl) ester (DEHP), CAS No. 117-81-7 (Tranche 4, ID 121). Sydney, NSW: National Industrial Chemicals Notification and Assessment Scheme. Accessed June 2014 at **http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessment-details?assessment_id=121**

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossiers. Available: **http://echa.europa.eu/information-on-chemicals/registered-substances**

Saillenfait AM, Gallissot F, Sabate JP. 2009. Differential developmental toxicities of di-n-hexyl phthalate and dicyclohexyl phthalate administered orally to rats. Journal of Applied Toxicology 29:510-21

Scientific Committee on Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP). 2004. Opinion concerning chemical ingredients in cosmetic products classified as carcinogenic, mutagenic or toxic to reproduction according to the Chemicals Directive 67/548/EEC. Adopted during the 28th Plenary meeting of 25 May 2004

SPIN (Substances in Preparations in Nordic Countries) Database. Available: **http://195.215.202.233/DotNetNuke/default.aspx**

The Poisons Standard (the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)). Available: **http://www.comlaw.gov.au/Details/F2013L01607/Download**

United States Environmental Protection Agency (US EPA). 2012a. Phthalates Action Plan. Revised 03.14.2012. Accessed February 2014 at **http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/phthalates_actionplan_revised_2012-03-14.pdf**

United States Environmental Protection Agency (US EPA). 2012b. Endocrine disruptor screening program, Universe of chemicals for potential endocrine disruptor screening and testing. Accessed February 2014 at **http://www.epa.gov/endo/pubs/edsp_chemical_universe_list_11_12.pdf**

United States Household Products Database. US National Library of Medicine. Available: **http://householdproducts.nlm.nih.gov/**

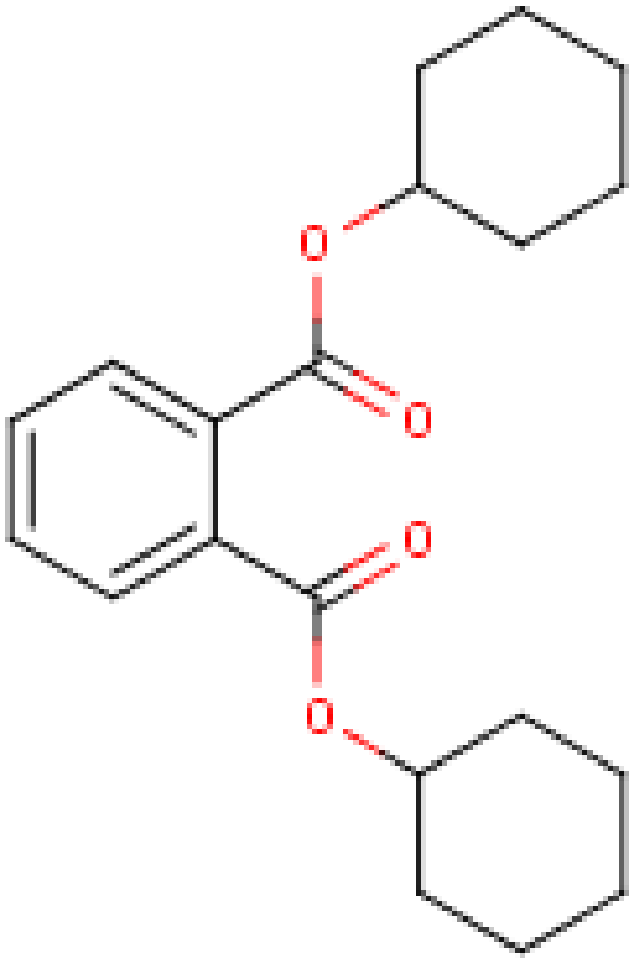
Wormuth M, Scheringer M, Vollenweider M, Hungerbuhler K. 2006. What are the sources of exposure to eight frequently used phthalic acid esters in Europeans? Risk Analysis 26:803-24

Yamasaki K, Takahashi M, Yasuda M . 2005. Two-generation reproductive toxicity studies in rats with extraparameters for detecting endocrine disrupting activity: introductory overview of results for nine chemicals. Journal of Toxicological Sciences 30:1-4

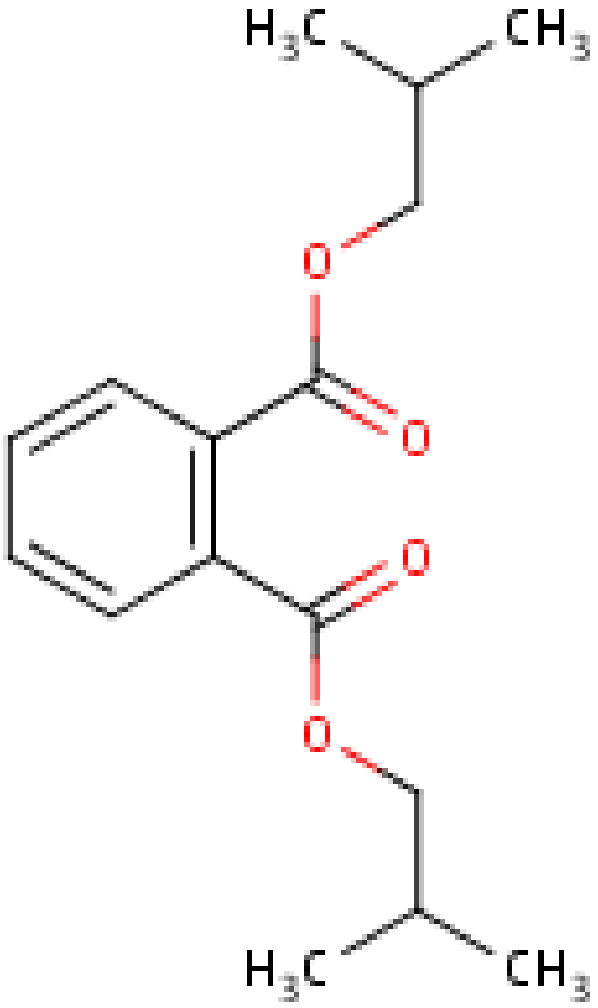
Last Update 21 April 2016

Chemical Identities

Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, dicyclohexyl ester** DcHP dicyclohexyl phthalate cyclohexyl phthalate phthalic acid, dicyclohexyl ester
CAS Number	84-61-7
Structural Formula	

	
Molecular Formula	C20H26O4
Molecular Weight	330.42

Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester** DiBP diisobutyl phthalate di(2-methylpropyl) phthalate phthalic acid, diisobutyl ester di(isobutyl)-1,2-benzenedicarboxylate
CAS Number	84-69-5
Structural Formula	

	
Molecular Formula	C16H22O4
Molecular Weight	278.35

Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, dibutyl ester** DBP dibutyl phthalate di-n-butyl phthalate phthalic acid, dibutyl ester dibutyl 1,2-benzenedicarboxylate
CAS Number	84-74-2
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	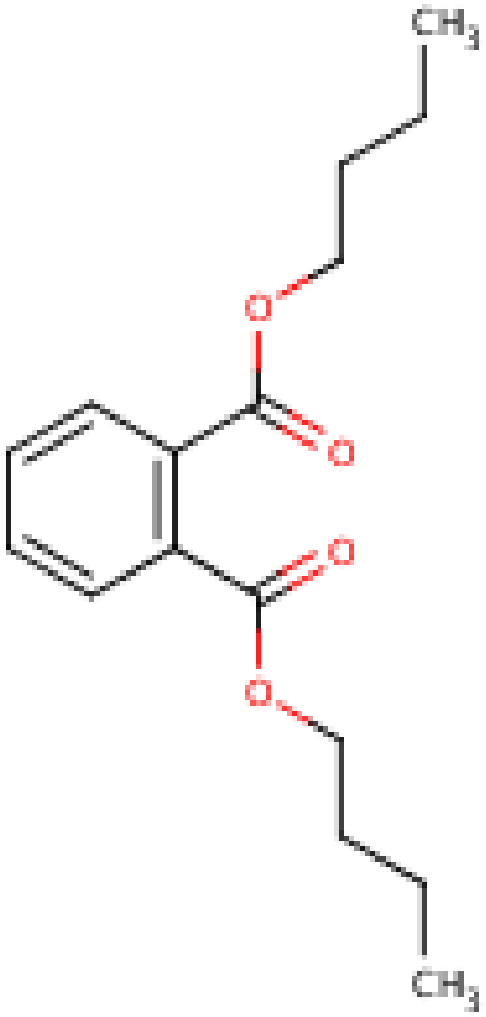
Molecular Formula	C16H22O4
Molecular Weight	278.35

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CAS Number	84-75-3
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	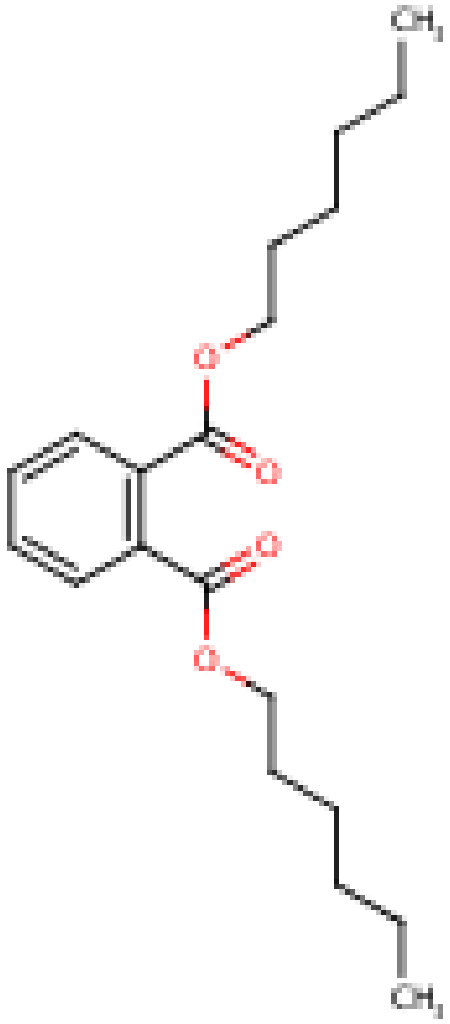
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Molecular Weight	334.45

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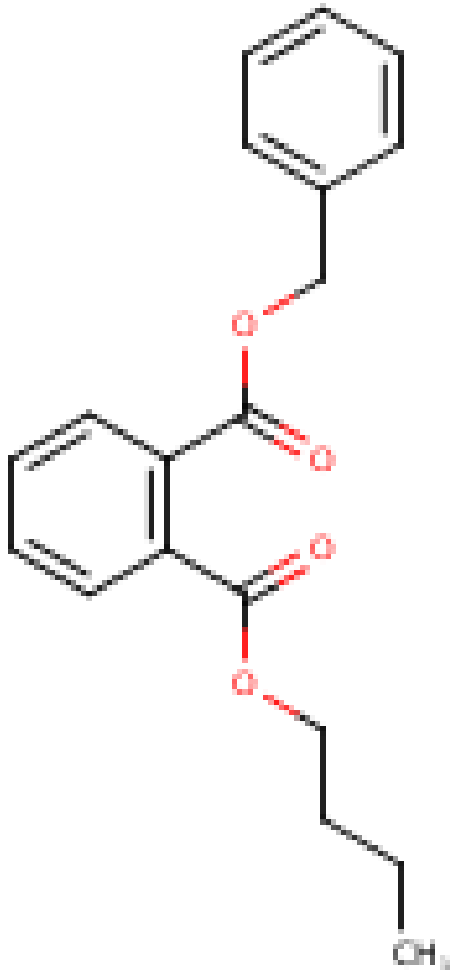
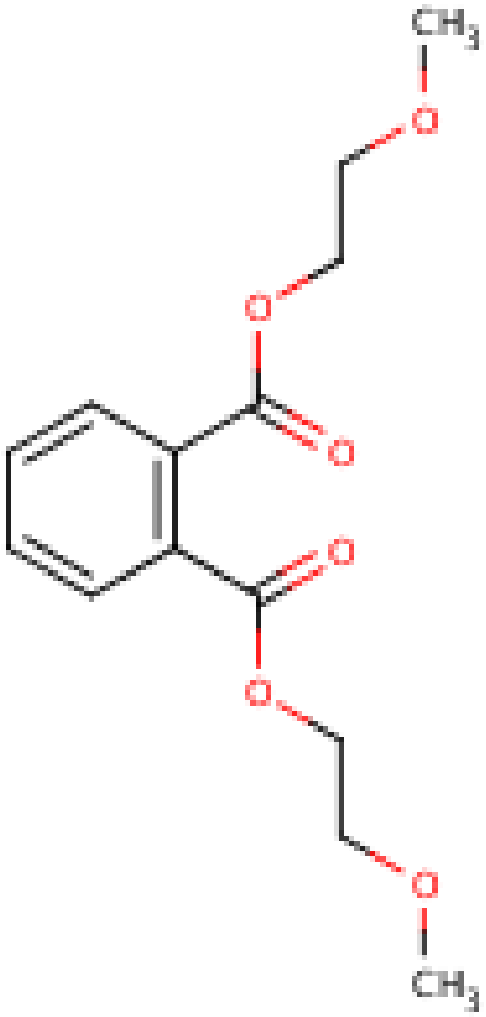
Structural Formula	

	
Molecular Formula	C19H20O4
Molecular Weight	312.36

Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, bis(2-methoxyethyl) ester** DMEP di(methoxyethyl) phthalate phthalic acid, bis(2-methoxyethyl) ester di(methylglycol) phthalate
CAS Number	117-82-8
Structural Formula	

	
Molecular Formula	C14H18O6
Molecular Weight	282.29

Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, di-C7-11-branched and linear alkyl esters** D711P dialkyl(C7-11-branched and linear) phthalate di(heptyl, nonyl, undecyl) phthalate phthalic acid, dialkyl (C7-C11) ester
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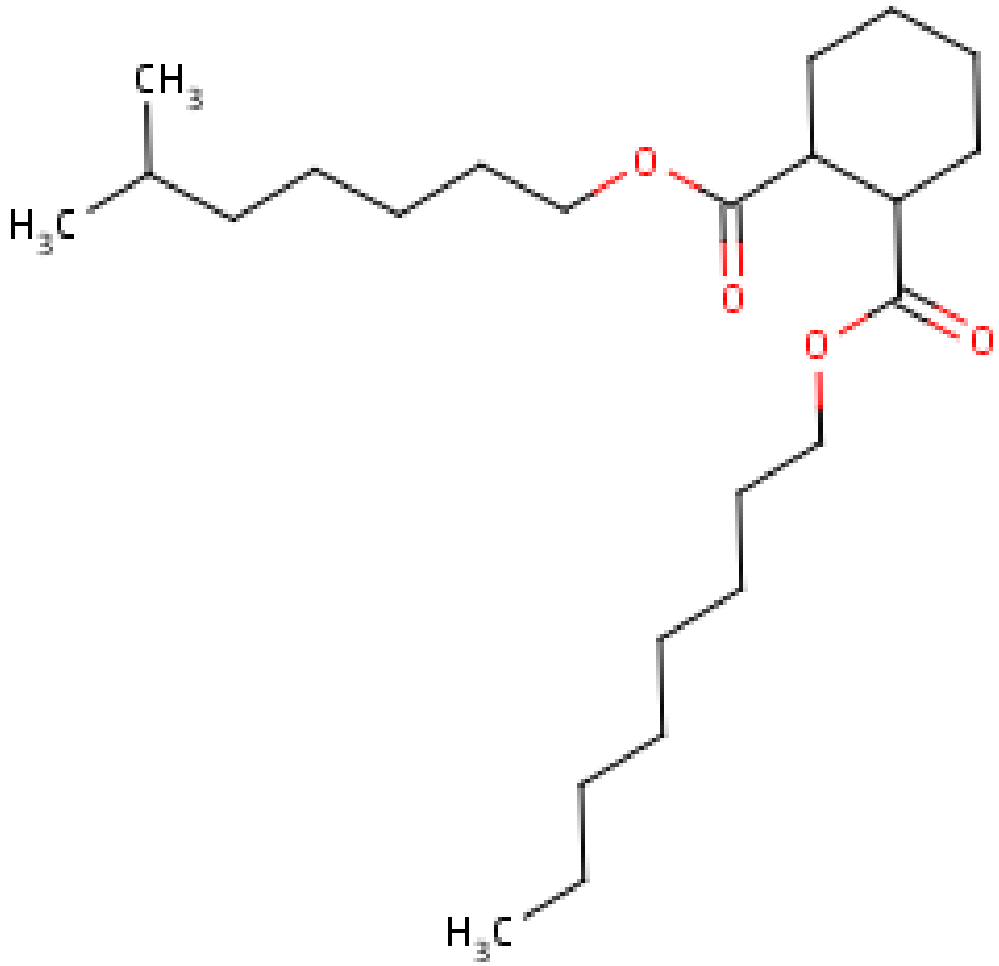
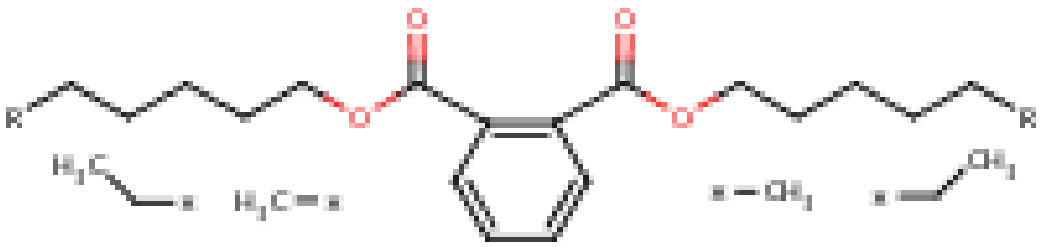
	
Molecular Formula	Unspecified
Molecular Weight	396.32

Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7 rich** DiHepP diisoheptyl phthalate C7-rich di-C6-8-branched alkyl phthalates
CAS Number	71888-89-6
Structural Formula	

	
Molecular Formula	Unspecified
Molecular Weight	392.58

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