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

10 March 2017

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,2-Benzenedicarboxylic acid, monobutyl ester	131-70-4
1,2-Benzenedicarboxylic acid, mono(phenylmethyl) ester	2528-16-7
1,2-Benzenedicarboxylic acid, mono(2-ethylhexyl) ester	4376-20-9

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**

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals assessed in this report are monoester metabolites of C4–6 side-chain transitional diester phthalates (NICNAS; NICNAS, 2010). The diester phthalates are metabolised to form the toxicologically active phthalate monoesters. The ester side-chain in monobutyl phthalate (MBP) is linear, whilst it is ring-structured in monobenzyl phthalate (MBzP) and branched in monoethylhexyl phthalate (MEHP). The chemical MBP is considered a biologically active metabolite of both dibutyl phthalate (DBP; CAS No. 84-74-2) and butyl benzyl phthalate (BBP; CAS No. 85-68-7). The chemical MBzP is an active metabolite of BBP. The chemical MEHP is a metabolite of diethylhexyl phthalate (DEHP; CAS No. 117-81-7) (NICNAS, 2010; 2013; 2015). The toxicokinetics, particularly metabolic profiles of MBP and MEHP, have been demonstrated to be comparable to that of their respective diester compounds (Lhuguenot et al., 1985; Mittermeier et al., 2016).

For toxicological endpoints where the data are incomplete or unavailable, information from the respective parent diester phthalates is used to examine the potential toxicity of the monoester phthalates.

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified.

International

The following international uses have been identified through Galleria Chemica and the US Environmental Protection Agency Aggregated Computational Toxicology Resource (ACToR).

The chemicals have no reported cosmetic, domestic or commercial uses.

The chemical MBP has a reported site-limited use as an intermediate in chemical synthesis.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

The chemicals are not listed in the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available for MEHP or MBzP.

The following exposure standards are identified for MBP (Galleria Chemica):

Time-weight average (TWA) = 3 mg/m^3 (Estonia; Denmark; Russia; Sweden)

Short-term value = 5 mg/m^3 (Estonia; Sweden)

Health Hazard Information

Toxicokinetics

Although the toxicokinetics of the parent diester phthalates (BBP, DBP and DEHP) are reasonably well studied, data on the monoester phthalates are limited. Through read-across from their parent chemicals and the available metabolism and excretion

data, the monoester chemicals are expected to be rapidly and almost completely absorbed and have widespread distribution into tissues following oral exposure. The chemicals are also rapidly metabolised and predominantly excreted in the urine.

In rats and hamsters, the total urinary recovery was almost complete after three days, up to 80 % and 95 % respectively, following multiple oral dosing (50 or 500 mg/kg bw/day MEHP). In humans, the amount detected in a 46-hour urine collection was 62 % and 100 % after a single oral dose of either 50 µg/kg bw MEHP or 10 µg/kg bw MBP, respectively. Furthermore, these metabolic profiles of MEHP and MBP have been demonstrated to be comparable to those of their respective parent diesters, although the metabolism can be dose, time and species dependent (Lhuguenot et al., 1985; 1988; Mittermeier et al., 2016). Glucuronidation is typically the main detoxification process for the monoesters (Mittermeier et al., 2016; NICNAS, 2015).

No toxicokinetic information is available for the chemicals by other routes of exposure.

Acute Toxicity

Oral

The available data are considered insufficient for hazard classification of the chemicals.

The oral median lethal dose (LD50) in rats was reported to be 1340 mg/kg bw for MEHP. Both MBzP and MBP had no reported LD50 information. The lowest oral lethal doses (LDLo) in mouse were 1600 mg/kg bw for MBP and 1850 mg/kg bw for MBzP (Galleria Chemica).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Skin Irritation

The available data are considered insufficient for skin irritation classification of the chemicals.

Eye Irritation

The available data are considered insufficient for eye irritation classification of the chemicals.

Sensitisation

Skin Sensitisation

The available data are considered insufficient for skin sensitisation classification of the chemicals.

The Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation Annex III includes MEHP as a suspected skin sensitiser based on (quantitative) structure activity-relationship (Q)SAR model.

No information is available on the skin sensitising property of MBP.

Repeated Dose Toxicity

Oral

Limited data are available. The most common systemic effects of the monoester phthalates were changes in liver weight, body weight loss or decreased weight gain, which may be chemical dependent. A number of lowest published toxic doses (TDLos) were reported for the chemicals in Galleria Chemica. However, it is unclear whether the data were daily doses or total doses over the specified experimental period.

The most common systemic target organs observed in repeated dose toxicity studies using the parent C4–6 diester phthalates were also the liver and kidney. For some of the diester phthalates, liver and kidney effects, when related to peroxisome proliferation or a rodent-specific mode of action, were unlikely to be relevant for a human health risk assessment (NICNAS).

Dermal

No data are available.

Inhalation

No data are available for MBP and MBzP.

Limited data are available for MEHP. Although Galleria Chemica reported lowest toxic concentration (TCLo) for MEHP as 30 mg/L/14 weeks for increased immune response, and 400 mg/L/14 weeks for biochemical changes and inflammatory effects, no further data are available and it is unclear whether the doses were daily doses or the total doses over the specified experimental period.

Overall, the data are considered insufficient to support a conclusive hazard classification.

Genotoxicity

Based on the weight of evidence, the monoester chemicals are not expected to have mutagenic or genotoxic potential in humans.

No data are available for MBP and MBzP. Limited data are available for MEHP.

The chemical MEHP was shown to cause chromosome aberration in vitro (in rat liver cells, mouse Leydig carcinoma cells, Chinese hamster ovary (CHO) and human prostate cancer cells) and DNA damage in comet assays (Erkekoglu & Kocer-Gumusel, 2014; Phillips et al., 1982; 1986). However, the chemical was negative in a sister chromatid exchange and a mutation test in CHO cells (Phillips et al., 1982). In addition, the International Agency for Research on Cancer (IARC, 2013) has reviewed DEHP extensively and did not regard it as a non-genotoxic carcinogen.

Carcinogenicity

The available data are considered insufficient for carcinogenicity classification of the chemicals.

The REACH Regulation Annex III includes MEHP and MBP as suspected carcinogens, based on the (Q)SAR model. Also, the parent diester phthalate, DEHP, is classified within the hazard category Carcinogenicity 1B (H350 'May cause cancer') in HCIS (Safe Work Australia).

However, no definitive evidence is available to indicate the carcinogenic potential of the monoesters in humans.

Reproductive and Developmental Toxicity

Toxicokinetic data have indicated that the chemicals are biologically active metabolites of the C4–6 transitional phthalates, which have been well characterised for reproductive and developmental toxicity (NICNAS; NICNAS, 2010; 2013; 2015). The data below also demonstrate that the monoester and diester phthalates within the chemical category have comparable toxicity profiles. On this basis, the three monoester phthalates are recommended for the same classifications as those of their respective parent compounds (see **Recommendation** section).

Comparable data on testicular or fertility-related toxicity of the monoester versus diester chemicals are limited. Atrophic changes of rat testes were reported at similar repeated oral doses of MBP (855 mg/kg bw/day), MBzP (985 mg/kg bw/day) and BBP (800 mg/kg bw/day) (see NICNAS, 2015 for review).

The monoester and diester phthalates, when administered orally under comparable experimental conditions, showed similar potencies for developmental effects both in vivo and in vitro regardless of the endpoint considered. The chemical MEHP and its parent compound, DEHP, had similar maternal and developmental toxicity effects at approximately equimolar doses, although MEHP caused more prenatal mortality, whereas DEHP produced greater foetal growth retardation and malformations (see Kavlock et al., 2002 for review). Also, the relative ranking of in vivo and in vitro potency were found similar among all chemicals within the category, except for MEHP (which was highly toxic in vitro compared with in vivo data, possibly due to kinetic differences between phthalates) (Janer et al., 2008).

Embryolethal and teratogenic effects of MBP, MBzP and their parent chemical BBP were comparative in vivo and in vitro (whole embryo culture study) after a single gavage dose in early organogenesis (i.e. on GD 8 in mice and on GD 10 in rats). Statistical significance was demonstrated in this study only in mice and not in rats for reproductive parameters (such as decreased live foetuses/litter, increased resorptions/litter, increased post-implantation loss/litter and decreased foetal weight) (Saillenfait et al., 2003).

The chemicals MBP, MBzP, MEHP and the corresponding diester phthalates demonstrated similar modes of action based on similarity in time-dependency to manifest foetal toxicity and malformations (NICNAS, 2010; 2013; 2015).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is adverse effects on fertility and development.

Public Risk Characterisation

Given the identified uses, it is unlikely that the public will be exposed to the chemicals. Hence, the public risk from these chemicals is not considered to be unreasonable.

Occupational Risk Characterisation

Given the critical long-term 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 chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) (see **Recommendation** section).

NICNAS Recommendation

Assessment of these chemicals are considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

On the basis of comparable reproductive and developmental toxicity profiles, the same classifications as those of the parent compounds are recommended for the monoester chemicals.

Under the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), the chemicals are recommended for classification as a Reproductive Toxicant Category 1B.

Note: For MEHP, the risk phrase is H360FD ‘May damage fertility. May damage the unborn child’. For MBzP and MBP, the risk phrase is H360Df ‘May damage the unborn child. Suspected of damaging fertility’.

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

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Not Applicable	May damage fertility. May damage the unborn child - Cat. 1B (H360FD) 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 oral and inhalation 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 chemicals are used. Examples of control measures that could 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 chemicals, if valid techniques are available to monitor the effect on the worker's health;
- 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 help meet 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 these chemicals has not been undertaken as part of this assessment.

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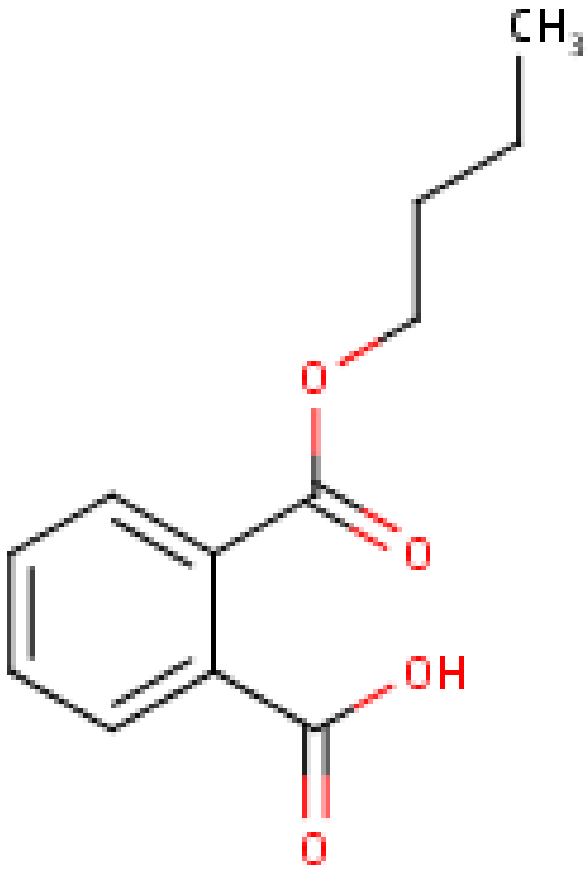
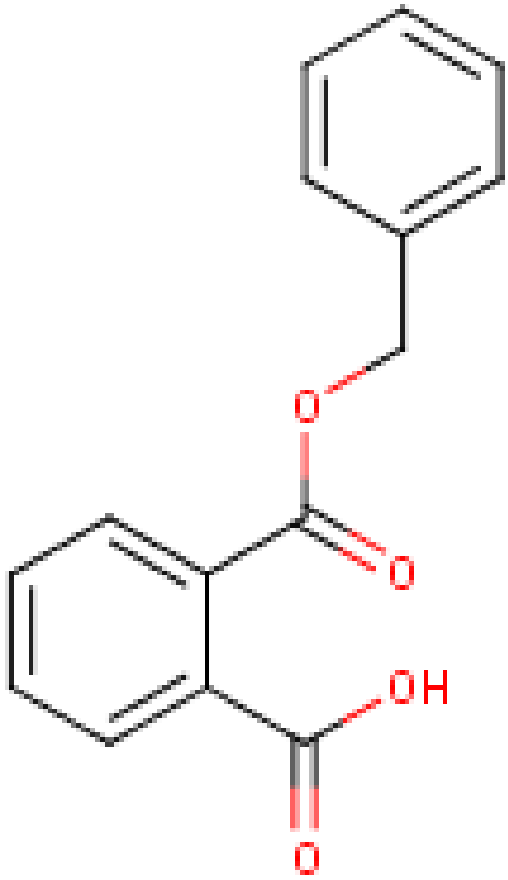
Last Update 10 March 2017

Chemical Identities

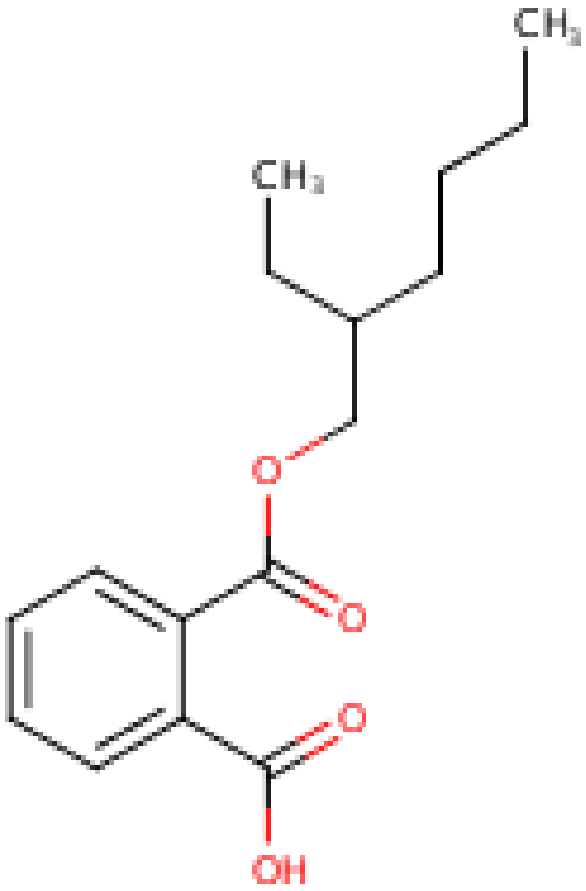
Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, monobutyl ester** MBP monobutyl phthalate

	butyl hydrogen phthalate phthalic acid, monobutyl ester 2-(butoxycarbonyl)benzoic acid
CAS Number	131-70-4
Structural Formula	
Molecular Formula	C12H14O4
Molecular Weight	222.2386

Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, mono(phenylmethyl) ester** MBzP monobenzyl phthalate benzyl hydrogen phthalate phthalic acid, benzyl ester 2-[(benzyloxy)carbonyl]benzoic acid
CAS Number	2528-16-7
Structural Formula	

	
Molecular Formula	C15H12O4
Molecular Weight	256.2558

Chemical Name in the Inventory and Synonyms	**1,2-Benzenedicarboxylic acid, mono(2-ethylhexyl) ester** MEHP monoethylhexyl phthalate (2-ethylhexyl) hydrogen phthalate phthalic acid, mono-(2-ethylhexyl) ester 2-{[(2-ethylhexyl)oxy]carbonyl}benzoic acid
CAS Number	4376-20-9
Structural Formula	

	
Molecular Formula	C16H22O4
Molecular Weight	278.3458

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