Phosphoric acid, dibutyl ester: Human health tier II assessment

28 June 2019

CAS Number: 107-66-4

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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.

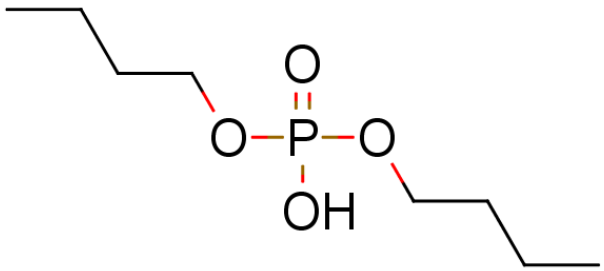
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	dibutyl phosphate di-n-butyl hydrogen phosphate dibutyl acid phosphate dibutyl hydrogen phosphate
Structural Formula	
Molecular Formula	C8H19O4P
Molecular Weight (g/mol)	210 210.21
Appearance and Odour (where available)	pale-amber odorless liquid
SMILES	C(CCC)OP(=O)(O)OCCCC

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified via European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) Dossiers, the Substances in Preparations in the Nordic countries (SPIN) database, in the Association Advancing Occupational and Environmental Health (ACGHI) publication, and in the Organisation for Economic Cooperation and Development Initial Assessment Report (OECD SIDS)**.**

The chemical has reported commercial uses in:

- cleaning and washing agents (with no evidence of use in domestic products);
- paints, lacquers and varnishes;
- lubricants and additives;
- antifoaming agents;
- antistatic formulations for textiles;
- pH regulators; and
- water treatment products.

While some of these uses could have application in the domestic setting, the chemical is not listed in the US Department of Health & Human Services Household Products Database (US HPD) and the REACH dossier does not list any domestic use for the chemical.

The chemical has site-limited use in metal separation and extraction processes.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is not listed on the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Exposure Standards

Australian

The chemical has an exposure standard of 8.6 mg/m³ (1 ppm) time weighted average (TWA) and 17 mg/m³ (2 ppm) short-term exposure limit (STEL).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 5–8.7 mg/m³ (1 ppm) TWA and 10–17 mg/m³ (2 ppm) STEL in different countries such as the USA (California, Hawaii, Minnesota), Canada (Yukon), Norway and Ireland.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) of 0.6 ppm (5 mg/m³) time weighted average (TWA).

Health Hazard Information

Dibutyl phosphate (DBP), is structurally related to tributyl phosphate (TBP), and is the major urinary metabolite of TBP (see **Toxicokinetics** section). Therefore, data from toxicological studies with TBP are used to support some of the assessment conclusions.

Toxicokinetics

Limited toxicokinetic information is available for the chemical.

When a single dose of the chemical was intraperitoneally (i.p.) administered to male rats at 250 mg/kg bw, it was mainly excreted unchanged in the urine (~ 48 %). Metabolites found in the urine were of very low concentration (0.1 % or less of the administered dose). The rest of the dose was not accounted for (Suzuki, 1984; Health Council of the Netherlands, 2004).

The chemical is the major urinary metabolite of tributyl phosphate (TBP) (CAS No. 126-73-8), previously assessed under the IMAP Program (NICNAS). After i.p. administration of a single dose of TBP (250 mg/kg bw), it was almost completely metabolised, with the major metabolites being DBP (~18 %) and monobutyl dihydrogen phosphate (~4 %) (Health Council of the Netherlands, 2004; Suzuki, 1984).

Acute Toxicity

Oral

Based on the reported median lethal doses (LD50) in experimental animals, the chemical has low acute oral toxicity. The reported median lethal doses (LD50) from 1 Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401 study and 1 non-guideline study in rats are >2000 mg/kg bw/day. Reported signs of toxicity included decreased locomotor activity, deep breathing, salivation, ptosis and red urine (OECD SIDS, 1994; JECDB; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Corrosion / Irritation

Corrosivity

Based on the available data, the chemical is corrosive to skin. Corrosive chemicals are also considered to cause irreversible effects on the eyes; the available eye irritation data for the chemical support this finding. Therefore, hazard classification for skin corrosion and serious eye damage is warranted (see **Recommendations** section).

Skin effects

In an in vitro study performed according to OECD TG 431, 50 µL of the chemical (neat) was applied to reconstructed human epidermis for 3 or 60 minutes. The mean tissue viability was 64.4 % and 1.8 % after 3 and 60 minutes, respectively. Substances that reduce viability to less than 15 % after 60 minutes are classified as corrosive. Therefore, the chemical is considered corrosive to skin (REACH).

In a non-guideline study in New Zealand White (NZW) rabbits, 500 µL of the chemical was applied to the inner surface of the ear (semi-occlusively) for 1, 2, 4 or 8 hours followed by observation for 7 days. Exposure to the chemical for up to 4 hours caused erythema (scores; 1–1.7 out of 4), but no oedema. After 8 hours exposure, an erythema score of 1.7 out of 4 and oedema score of 0 was reported. The effects were fully reversible after the 1–4 hour treatments, but not after the 8 hour exposure (REACH). Information on number or scores of individual animals was not available.

Eye effects

In a non-guideline study in 2 rabbits, 100 µL of the chemical was applied into the conjunctival sac of the eye. Observations were made at 24, 48, 120 hours and after 7 days. The average score was 1.5 out of 4 for cornea opacity, 1 out of 2 for iris irritation, 2 out of 3 for conjunctival redness and 2.8 out of 4 for chemosis. None of the effects were fully reversible within 7 days (REACH).

Observations in humans

Workers exposed to the chemical complained of respiratory irritation (HSDB; REACH). Due to the acidic nature of the chemical it may cause irritation to nose, throat and lungs (ACGIH, 2009). Reported experimental pH of 1.4 and pKa of 1.0–1.7 at 25°C indicate that the chemical is a relatively strong acid (REACH). pKa is term used to describe the strength of an acid values—lower values indicate stronger acids.

Sensitisation

Skin Sensitisation

Based on the available animal data from a guideline study, low concentrations of the chemical are not expected to cause skin sensitisation. Due to the corrosive nature of the chemical repeated exposure to high concentrations of the chemical is unlikely to occur (see **Corrosivity** section).

In a guinea pig maximisation test (GPMT) in female Hartley guinea pigs (10 treated and 5 controls), intradermal induction was performed using 1.0 % DBP in water and dermal induction with 10 % DBP in water, followed by challenge with 2 % DBP in water. No skin reactions were observed during the study and the chemical was therefore considered to be negative for skin sensitisation (REACH).

Repeated Dose Toxicity

Oral

Based on the available data, the chemical can cause dose-dependent bladder effects including irritation, inflammation and epithelial hyperplasia in rats. These effects are very similar to those of the carcinogenic parent chemical TBP (NICNAS), and are considered to indicate carcinogenic properties of the chemical, as they may contribute to the development of bladder cancer (see **Carcinogenicity** section). Available information indicates that the chemical does not to cause other serious damage to human health. In the absence of more severe non-neoplastic bladder effects, hazard classification for repeated dose toxicity is not warranted.

In a combined repeated dose toxicity study with reproduction/developmental toxicity screening test, conducted in accordance with OECD TG 422, Sprague Dawley (SD) rats (10/sex/dose) were orally administered (gavage) 0, 30, 100, 300 or 1000 mg/kg bw/day of the chemical, from 2 weeks before the start of mating. Males were treated for a total 44 days and females for 40–51 days (until 3 days postpartum lactation).

Mortality occurred in both males and females receiving the highest dose (3 males; 5 females), as well as 2 females receiving 300 mg/kg bw/day and 3 females receiving 100 mg/kg bw/day. All rats receiving 30 mg/kg bw/day survived the study. Clinical signs of toxicity included low locomotor activity, deep breathing, soft stools and poor coat appearance. Body weight gain was reduced in both sexes at the highest dose. Food consumption was slightly reduced in males during the first week of the study. Urinalysis, haematological analysis and organ weight were unchanged apart from absolute and relative liver weight in high dose females.

The most significant histological effect was hyperplasia of the bladder epithelium and degeneration of the bladder mucosa in rats receiving ≥100 mg/kg bw/day and ulcers at the 2 highest doses. Thickening of the anterior gastric mucosa of the stomach occurred at ≥300 mg/kg bw/day. A few high dose females had enlarged liver cells (4 rats) and focal necrosis (2 rats). Excretion of red urine and contamination of the lower abdominal hair was considered related to the damage in the bladder. A no observed adverse effect level (NOAEL) of 30 mg/kg bw/day was reported based on mortality and bladder damage at doses ≥100 mg/kg bw/day (JECDB; REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available negative results of several genotoxicity studies (both in vitro and in vivo), the chemical is not expected to be genotoxic.

In vitro

The chemical was:

- negative in point mutation studies in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA 1537, and *Escherichia Coli* WP2 uvrA at concentrations up to 156.2 µg/plate, with and without metabolic activation (REACH);
- negative in a hypoxanthine-guanine phosphoribosyltransferase (HPRT) gene mutation assay in Chinese hamster lung fibroblasts at concentrations up to 2200 µg/mL for 4 hours with and without metabolic activation, and for 24 hours without metabolic activation (REACH); and
- negative in a chromosome aberration assay in Chinese hamster lung cells at concentrations up to 410 µg/mL without metabolic activation and 540 µg/ml with metabolic activation (REACH).

In vivo

The chemical was negative in an OECD TG 474 micronucleus test using Naval Medical Research Institute (NMRI) mice (5/sex/dose). Two mortalities and reduced motor activity were observed at the highest dose. No significant increases in micronucleated polychromatic erythrocytes were observed at 24, 48 hours and 72 hours after oral administration (gavage) of the chemical at 100, 300, or 1000 mg/kg bw/day for 2 days (REACH).

Carcinogenicity

There are no carcinogenicity studies available for the chemical. Based on the available data from repeat dose toxicity studies (see **Repeated Dose Toxicity: Oral** section) and the available data on TBP which has DBP as its major urinary metabolite (NICNAS), the chemical is expected to have carcinogenic properties, warranting hazard classification (see **Recommendations** section).

TBP is classified as hazardous, Carcinogenicity – Category 2; H351 (Suspected of causing cancer) in the HCIS (Safe Work Australia) based on studies in rats and mice (NICNAS). Therefore, hazard classification for the chemical DBP is also warranted.

Non-neoplastic bladder damage by oral intake of the chemical (see **Repeated dose toxicity: Oral** section) is similar to bladder damage caused by TBP (NICNAS). TBP is almost completely metabolised in the rat prior to urinary excretion and the chemical was identified as the major metabolite (see **Toxicokinetics** section). Hence, it is highly likely that the chemical makes a major contribution to the bladder effects seen in studies with TBP.

In a 24 month carcinogenicity study, SD rats (50/sex/dose) received TBP in diet (200–3000 ppm) equivalent to 8.9, 32.5 or 143.3 mg/kg bw/day for males and 11.6, 42.0 or 181.5 mg/kg bw/day for females. The incidence of papillomas of the urinary bladder was significantly increased in males and females receiving the highest dose. Transitional cell carcinomas were observed in the bladder of males (6/49) and females (2/50) at the highest dose. Dose-related increases in the incidence and severity of urinary bladder hyperplasia were observed in male and female rats. Increased incidences of hepatocellular adenomas in male and females rats were not statistically significant; however, in male high dose rats the incidence was outside the range of the historical controls (NICNAS).

In a 24-month carcinogenicity study, CD-1 mice received TBP in diet (150–3500 ppm) equivalent to 24, 169 or 585 mg/kg bw/day for males and 29, 206 and 711 mg/kg bw/day for females. Mortality was increased in high dose males. A dose-dependent increase in the incidence of hepatocellular adenomas was observed in male mice (3/50, 6/50, 7/50, 10/50), and this reached statistical significance at the highest dose. A few liver adenomas were observed in females receiving the high dose of TBP (NICNAS).

Reproductive and Developmental Toxicity

The chemical does not cause specific reproductive or developmental toxicity. Any developmental effects were only observed secondary to maternal toxicity.

In a combined repeated dose toxicity study with reproduction / developmental toxicity screening test (see **Repeated dose toxicity: Oral** section) in SD rats, there was no significant effect on fertility, reproductive performance or adverse effects on reproductive organs. At the highest dose (1000 mg/kg bw/day), there was a decrease in the number of live pups. Dose related toxicity in the parents was observed from 100 mg/kg bw/day (see **Repeated dose toxicity: Oral** section). The NOAEL for reproductive toxicity is 1000 mg/kg bw/day for both sexes. The NOAEL for developmental toxicity is 300 mg/kg bw/day based a decrease in the number of live pups at 1000 mg/kg bw/day (JECDB; REACH).

In a developmental toxicity study, pregnant rats were orally treated (gavage) with 250, 500, or 1000 mg/kg bw/day on days 7–17 of gestation. There was no evidence of maternal or foetal toxicity (Proctor & Hathaway, 2004). No further information was available.

Other Health Effects

Neurotoxicity

Limited information is available.

Delayed neurotoxicity was reported in a study in chickens receiving daily dermal applications of the chemical at 100 mg/kg bw day for 90 days (Abou-Donia et al., 1981; REACH). No further information is available.

The related chemical TBP (see **Toxicokinetics** section), did not induce delayed neurotoxicity in a 42 day oral gavage study where chickens received TBP at 1500 mg/kg bw twice a day, on day 0 and 21 (NICNAS; REACH). Effects of TBP on acetyl cholinesterase were minor and only occurred at high doses (or were reversible) (NICNAS; REACH).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are the systemic long-term effects of carcinogenicity and local effects of corrosivity and potential for respiratory tract irritation.

Public Risk Characterisation

The uses of the chemical in Australia are unknown. The chemical is used overseas in a wide range of commercial products. However, the chemical is not expected to have frequent uses in products that could expose the public directly to the chemical. The chemical is not listed in the US Household Products Database and no consumer uses are listed in the REACH dossier.

It is expected that the chemical may be available bound within articles or coated surfaces, but consumers may be exposed to the chemical released from articles through, for example, abrasion or dissolution. While many phosphate esters are commonly detected in household dust, there is currently no evidence of the chemical being present in household dust (Cequier et al., 2014; He et al., 2018; Wong et al., 2018; Shoeib et al., 2019). The total levels of phosphate esters that have been measured in house dust are relatively low. The human exposure from indoor environments in Australia to 9 organophosphate esters was estimated to 14 ng/kg bw/day. Therefore, the chemical is not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

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

Given the critical systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. Good hygiene practices to minimise oral exposure are expected to be in place. The chemical 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 the chemical is 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

The chemical is recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. 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]
Irritation / Corrosivity	Not Applicable	Causes severe skin burns and eye damage - Cat. 1 (H314)
Carcinogenicity	Not Applicable	Suspected of causing cancer - Cat. 2 (H351)

[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 industry

Control measures

Control measures to minimise the risk from dermal, ocular and inhalation exposure to the chemical 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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- health monitoring for any worker who is at risk of exposure to the chemical, 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 chemical.

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 chemical 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 chemical has not been undertaken as part of this assessment.

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