Monobutyl phosphate: Human health tier II assessment

12 December 2019

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phosphoric acid, monobutyl ester	1623-15-0
Phosphoric acid, butyl ester	12788-93-1

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

These chemicals in this group are phosphoric acid, monobutyl ester (MBP; CAS No. 1623-15-0) and a commercial product identified as phosphoric acid, butyl ester (BP; CAS No. 12788-93-1). BP is an undefined mixture containing 10–80 %, MBP and dibutyl phosphate (DBP; CAS No. 107-66-4). The product also contains tributyl phosphate (TBP; CAS No. 126-73-8) (<10 %) (REACH). DBP and TBP have been assessed under IMAP previously (NICNASa; NICNASb). Since MBP is assumed to be a major component of BP, the chemicals are assessed together.

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: the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossiers; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); and the Agency for Toxic Substances and Disease Registry (ATSDR).

These chemicals have reported domestic uses, including in:

- cleaning/washing agents; and
- paints, lacquers and varnishes.

These chemicals are not listed in the US Household Products database (US HPD) or the American Cleaning Institute (ACI) database, indicating that domestic use of the chemicals may not be widespread.

These chemicals have reported domestic uses in the SPIN database. However, it should be noted that SPIN does not distinguish between direct use of the chemicals, or use of the materials that are produced from chemical reactions involving the chemicals.

The chemicals have reported commercial uses, including in:

- flame retardants and extinguishing agents;
- manufacture of wood products;
- lubricants and greases;
- colouring agents;
- construction materials; and
- welding and soldering agents.

The chemicals have reported site-limited uses in polymers and manufacturing of chemicals.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

These chemicals are not listed on 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.

Health Hazard Information

No hazard data are available for MBP. The experimental pKa of 1.6 at 25 ºC (OECD Toolbox 4.2) indicates that similar to DBP, MBP is a relatively strong acid. Therefore, the chemicals are expected to have similar local toxicological properties. Without knowing amount of MBP in BP mixture, it is difficult to draw any conclusions on systemic effects of MBP.

Toxicokinetics

No information is available on the absorption, distribution and excretion of the chemicals.

Based on the available data on other phosphate esters, the chemicals are expected be readily absorbed through the gastrointestinal tract (ATSDR, 2012; REACH). Based on the toxicokinetic study on phosphoric acid, 2-ethylhexyl ester, the chemicals are expected to be hydrolysed by esterases (phase-I metabolism) into phosphate and butyl alcohol. Urinary excretion is expected to be the main route of elimination (REACH).

Acute Toxicity

Oral

Based on the reported median lethal doses (LD50) in experimental animals, the chemicals are expected to have low acute toxicity following oral exposure. The reported LD50 values for BP and MBP in rats are >2000 mg/kg bw.

In 3 acute oral toxicity studies conducted similarly to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, the reported LD50 values for BP in rats were 5300, 2474 and 3800 mg/kg bw. Reported clinical signs of toxicity included closed eye lids, abnormal breathing, crouched posture, piloerection, decreased motor activity and red stained urine (REACH).

In an acute oral toxicity study in Sprague Dawley rats, the reported LD50 for MBP was >4640 mg/kg bw (3 out of 5 rats survived this dose). The only reported clinical toxicity sign was acute depression (Michigan Department of Environmental Quality, 2000).

Dermal

Based on the reported LD50 in experimental animals, BP is expected to have low acute toxicity following dermal exposure. No data are available for MBP.

In 2 acute dermal toxicity studies conducted similarly to OECD TG 402, the reported LD50 values for BP in rabbits were >2000 mg/kg bw. Reported clinical signs of toxicity included oedema, erythema, eschar, necrosis (REACH).

Inhalation

Based on the available data in experimental animals, BP is expected to have low acute toxicity following inhalation exposure. No data are available for MBP.

In an acute inhalation toxicity study conducted similarly to OECD TG 403, rats (10/sex/dose) were exposed to BP at 20.28 mg/L (aerosol) for 4 hours. No mortality occurred following exposure and no clinical signs of toxicity were reported (REACH).

Corrosion / Irritation

Corrosivity

Based on the available data, BP is corrosive to skin. Corrosive chemicals are also considered to cause irreversible effects on the eyes; the available eye irritation data for BP support this finding.

While no data are available for MBP, it is a strong acid with an experimental pKa of 1.6 at 25 ºC (which is lower than the measured pKa for BP). The pKa values is used to describe the strength of an acid values—lower values indicate stronger acids. Therefore, MBP is expected to be corrosive and hazard classification for skin corrosion and serious eye damage is warranted for both MBP and BP (see **Recommendation** section).

In an in vivo skin irritation study conducted according to OECD TG 404, 500 µL of undiluted BP was applied under occlusion to a white Russian rabbit for 4 hours. Severe erythema (grade 4), severe oedema (grade 4) and necrosis were observed 1 hour after application. The symptoms were not reversible within 14 days. No further animals were tested since the substance was corrosive. Under the test conditions, the chemical was considered corrosive to skin (REACH).

In an in vitro skin corrosion study conducted according to OECD TG 435 (in vitro membrane barrier test method for skin corrosion), 500 µL of BP was applied to discs in triplicates. The reaction time to break through the bio-barrier membrane and subsequently activate the underlying chemical detection system (CDS) was measured. The mean time to activate the CDS was between 3–60 min (~45 min). Based on the criteria of the assay, the chemical was considered corrosive to skin (REACH).

Slight to moderate eye irritation was reported in a non-guideline study after application of diluted BP (0.1–2 %) to rabbit eyes (REACH).

Sensitisation

Skin Sensitisation

No sensitisation data are available. Due to the corrosive nature of the chemicals, studies on sensitisation properties of the chemicals are unlikely to have been undertaken (see **Corrosivity** section).

Repeated Dose Toxicity

Oral

Based on the available data, BP is not expected to be harmful following repeated oral exposure, due to the reversibility of the effects. No data are available for MBP. However, as a major constituent of BP, it is expected that MBP is not significantly more toxic than BP.

In a 90-day oral toxicity study conducted according to OECD TG 404, Wistar rats (10/sex/dose) received BP via oral gavage at concentrations of 0, 50, 200 or 400 mg/kg bw/day, followed by 28 days without treatment. No mortality occurred during the study. No treatment-related clinical signs of toxicity were observed. Histopathology of organs (including bladder and kidneys) showed no effect of the chemical. Microscopic examination revealed abnormalities in non-glandular stomach of animals (both sexes) treated with 50, 200 or 400 mg/kg bw/day. These effects were attributed to the local irritating effects of the chemical and were considered non-adverse as complete recovery was observed at the end of 28 day recovery period. Minor changes in haematological, clinical biochemistry, body weight, feed consumption and urine analysis were considered incidental due to a lack of dose-dependency and accompanying macroscopic or histopathological effects. Under the test conditions, the reported no observed adverse effect level (NOAEL) was 400 mg/kg bw/day in rats (REACH).

In an oral repeated dose toxicity study conducted similarly to OECD TG 407, albino rats (10/sex/dose) received BP via oral gavage at concentrations 0 or 500 mg/kg bw/day for 15 times over 19 days. No significant treatment-related changes in clinical or histopathological findings (including kidneys) were observed. Under the test conditions, the reported NOAEL was 500 mg/kg bw/day in rats (REACH).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the negative results of several genotoxic studies (both in vitro and in vivo), BP is not expected to be genotoxic. No data are available for MBP; however, quantitative structure activity relationship (Q)SAR modelling for genetic toxicity using the OASIS TIMES software indicated that MBP was negative for in vitro mutagenicity (89 % in domain). As MBP is a major constituent of BP, the negative genotoxicity results for BP indicate that MBP is also not genotoxic.

In vitro

BP was negative in:

- a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA97a, TA98, TA100, TA102 and TA1535, with and without metabolic activation (S9) up to 5 µL/plate (unknown concentrations) (REACH);
- a bacterial reverse mutation assay in *S. typhimurium* strains TA100 and TA2638, with and without metabolic activation at concentrations up to 2000 µg/plate (REACH);
- a bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, with and without metabolic activation up to 10 µL/plate (unknown concentrations) (REACH);
- a bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2 uvrA, with and without metabolic activation at concentrations up to 156.2 µg/plate;
- a mammalian cell gene mutation study (OECD TG 476) in Chinese hamster lung fibroblasts (V79) with and without metabolic activation (concentrations used not reported) (REACH); and
- a chromosome aberration study (OECD TG 473) in Chinese hamster ovary (CHO) cells with and without metabolic activation (concentrations used not reported) (REACH).

In vivo

BP was negative in a micronucleus test (OECD TG 474) in Naval Medical Research Institute (NMRI) mice (5/sex/dose) receiving the chemical via oral gavage at concentrations of 100, 300 or 1000 mg/kg bw. Two mortalities and reduced motor activity were observed at the highest dose. No significant increases in micronucleated polychromatic erythrocyte (PCE) frequency were reported (REACH).

Carcinogenicity

No data are available for the chemicals.

The structurally related chemicals and components of BP, DBP and TBP were considered carcinogenic when they were assessed under IMAP (NICNASa; NICNASb). The carcinogenicity in these studies were preceded by bladder irritation and adverse histopathological findings. In repeated dose toxicity studies, BP containing MBP, DBP and TBP did not cause any adverse histopathology in bladder or other organs (see **Repeated dose toxicity** section), indicating that MBP may have less potential to cause carcinogenic bladder lesions than DBP and TBP.

Reproductive and Developmental Toxicity

Based on the available data, BP is not expected to cause specific reproductive or developmental toxicity. No data are available for MBP. However, as a major constituent of BP, it is expected that MBP is not significantly more toxic than BP.

In a prenatal developmental toxicity study conducted according to OECD TG 414, BP was administered by oral gavage at doses 0, 50, 200 or 400 mg/kg bw/day to pregnant Wistar rats (24/dose) during gestation days (GD) 5–19. No mortality occurred during the study. No treatment-related clinical signs were observed in any of the pregnant female animals. The body weight and feed consumption during gestation period in all treatment groups were comparable with the control group. The mean body weight gain (%) was slightly reduced in the high dose animals on GD 14 and 17. No significant treatment-related effects were observed in reproduction parameters (corpora lutea count, early and late resorption, pre- and post-implantation loss, foetal body weight, sex ratio, and litter size) at any dose level. Skeletal examination of foetuses indicated no treatment-related effects. Based on these observations, the NOAEL for maternal and foetal toxicity was 400 mg/kg bw/day (REACH).

Other Health Effects

Neurotoxicity

Neurotoxicity is a potential adverse effect of many organophosphates, but the potency levels that may cause neurotoxicity varies significantly. Based on the available data, BP is not expected to be neurotoxic. No data are available for MBP. However, as a major constituent of BP, it is expected that MBP is not significantly more toxic than BP.

In a sub-chronic oral toxicity study (see **Repeated dose toxicity**), neurobehavioural examination was undertaken, which included examination of sensory activity, grip strength and motor activity. No significant treatment-related neurobehavioural effects were reported (REACH).

Risk Characterisation

Critical Health Effects

The critical health effect for risk characterisation is the local effect of corrosivity.

Public Risk Characterisation

Although use in domestic products in Australia is not known, the chemicals are reported to be used in domestic products overseas. The data indicate that the majority of uses in domestic products that could expose the public directly to the chemicals, is not frequent or widespread. Therefore, the risk to the public posed by domestic products containing the chemicals is not considered to be unreasonable.

The public may be directly exposed via articles or coated surfaces containing the chemicals. While phosphate esters are retained well in intact articles, there is potential for them to be released if the article breaks down into smaller pieces or dust. The chemicals could be released from articles through abrasion or dissolution (ATSDR, 2012). While many phosphate esters are commonly detected in household dust, there is currently no evidence of BP or MBP being present in house 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 nine organophosphate flame retardants was estimated to 14 ng/kg bw/day. Therefore, the risk of adults and children being exposed to levels of these chemicals and subsequent adverse health effects is considered to be very low.

Should further information to better characterise exposure to BP and MBP become available, further assessment may be required.

Occupational Risk Characterisation

During product formulation, dermal and ocular 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 these chemicals at lower concentrations could also occur while using formulated products containing these chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the local health effects, these chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and ocular exposure are implemented. These 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 controls expected to be in place due to the corrosivity classification are expected to be sufficient to protect workers from any potential systemic effects.

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

NICNAS Recommendation

Assessment of these chemicals 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 chemicals are 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. 1B (H314)

[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 and ocular exposure to these 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 that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;

- 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 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 chemicals has not been undertaken as part of this assessment.

References

Agency for Toxic Substances and Disease Registry (ATSDR) 2012. Toxicological profile for phosphate ester flame retardants. Accessed November 2019 at **http://www.atsdr.cdc.gov/ToxProfiles/tp202.pdf**

Cequier E, Ionas C, Covaci A, Marcé RM, Becher G and Thomsen C, 2014. Occurrence of a broad range of legacy and emerging flame retardants in indoor environments in Norway. Environmental science&technology, 48(12) pp. 6827-6835.

Cleaning Product Ingredient Inventory, American Cleaning Institute (ACI). Accessed November 2019, **http://www.cleaninginstitute.org/science/ingredient_inventory.aspx**.

Galleria Chemica. Accessed November 2019 at **http://jr.chemwatch.net/galleria/**

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations 2009. Third edition. Accessed November 2019 at **http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html**

He C, Wang X, Thai P, Baduel C, Gallen C, Banks A, Bainton P, English K and Mueller JF, 2018. Organophosphate and brominated flame retardants in Australian indoor environments: Levels, sources, and preliminary assessment of human exposure. Environmental Pollution, 235 pp. 670-679.

Michigan Department of Environmental Quality, 2000, File for Monobutyl Phosphoric Acid (CAS No. 1623-15-0)

National Industrial Chemicals Notification and Assessment Scheme (NICNASa). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for phosphoric acid, dibutyl ester (CAS No. 107-66-4). Accessed November 2019 at **http://www.nicnas.gov.au**

National Industrial Chemicals Notification and Assessment Scheme (NICNASb). Inventory Multi-tiered Assessment and Prioritisation (IMAP) Human Health Tier II Assessment for phosphoric acid, tributyl ester (CAS No. 126-73-8). Accessed November 2019 at **http://www.nicnas.gov.au**

Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox Version 4.2.

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Phosphoric acid, butyl ester (CAS No. 12788-93-1). Accessed November 2019 at **https://echa.europa.eu/registration-dossier/-/registered-dossier/10566**

Safe Work Australia. Hazardous Chemical Information System (HCIS). Accessed November 2019 at **http://hcis.safeworkaustralia.gov.au/**

Shoeib T, Webster GM, Hassan Y, Tepe S, Yalcin M, Turgut C, Kurt-Karakus PB and Jantunen L, 2019. Organophosphate esters in house dust: A comparative study between Canada, Turkey and Egypt. Science of The Total Environment, 650 pp. 193-201.

Substances in Preparations in Nordic countries (SPIN) database. Accessed November 2019 at **http://www.spin2000.net/spinmyphp/**

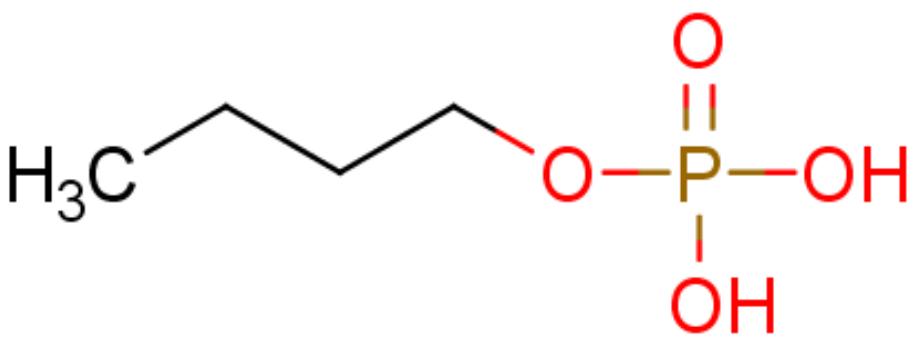
US Environmental Protection Agency's Aggregated Computational Toxicology Resource (ACToR). Accessed November 2019 at **https://actor.epa.gov/actor/home.xhtml**

US Household Products Database. US Department of Health and Human Services. Accessed November 2019 at **http://householdproducts.nlm.nih.gov/advancedsearch.htm**

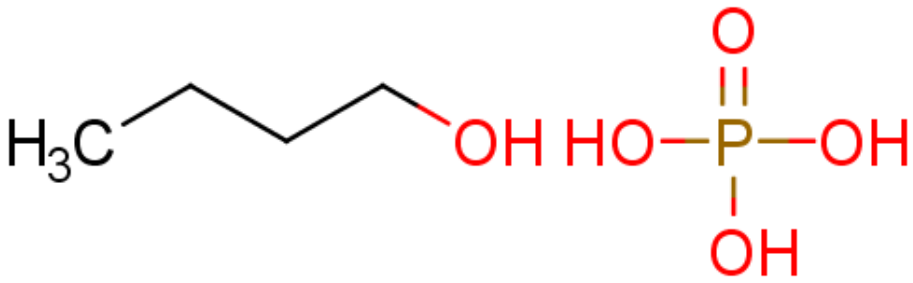
Wong F, de Wit CA and Newton SR, 2018. Concentrations and variability of organophosphate esters, halogenated flame retardants, and polybrominated diphenyl ethers in indoor and outdoor air in Stockholm, Sweden. Environmental Pollution, 240 pp. 514-522.

Last Update 12 December 2019

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, monobutyl ester** butyl dihydrogen phosphate monobutyl phosphate (MBP) butylphosphoric acid mono-n-butylphosphoric acid
CAS Number	1623-15-0
Structural Formula	

Molecular Formula	C4H11O4P
Molecular Weight	154.1

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, butyl ester** butyl dihydrogen phosphate butyl phosphate (BP) butan-1-ol, phosphoric acid n-butyl acid phosphate Hordaphos MDB
CAS Number	12788-93-1
Structural Formula	
Molecular Formula	C4H10O.xH3O4P
Molecular Weight	172.12

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