Phosphoric acid, tributyl ester: Human health tier II assessment

28 June 2019

CAS Number: 126-73-8

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.

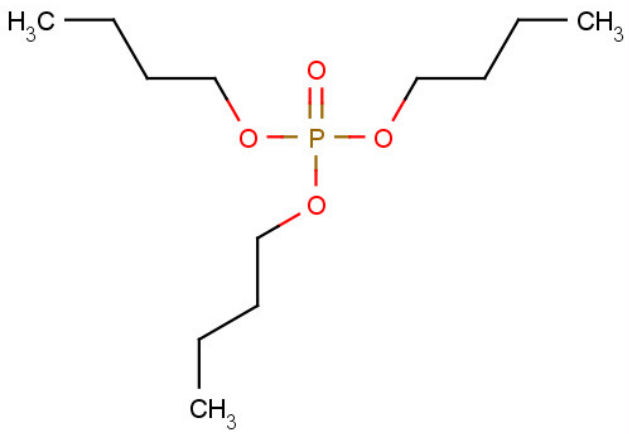
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	butyl phosphate tributyl phosphate (TBP) tri-n-butyl phosphate phosphoric acid, tribuyl ester
Structural Formula	
Molecular Formula	C12H27O4P
Molecular Weight (g/mol)	266.32
Appearance and Odour (where available)	Colourless, odourless liquid.
SMILES	C(CCC)OP(=O)(OCCCC)OCCCC

Import, Manufacture and Use

Australian

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

International

The following international uses have been identified via European Union (EU) Registration, Evaluation and Authorisation of Chemicals (REACH) Dossiers, Galleria Chemica, Government of Canada, and the Substances in Preparations in the Nordic countries (SPIN) database.

The chemical has reported commercial uses in:

- adhesives and binding agents;
- cleaning/washing agents (with no evidence of use in domestic products);
- colouring agents;
- corrosion inhibitors;
- fillers;
- paints, lacquers and varnishes;
- surface treatments;
- surfactants;
- hydraulic fluids and additives;
- building materials;
- antifoaming agents;
- flame retardants;
- reprographic agents;
- softeners; and
- solvents.

While some of these categories of use could have application in the domestic setting, frequent use is not expected. The chemical is only listed once in US Department of Health & Human Services Household Products Database (US HPD) for use in one auto care product (brake fluid) at a concentration of 2 %.

The Organisation for Economic Cooperation and Development Screening Information Data Set Initial Assessment Report (OECD SIAR) stated that there are no known consumer products containing the chemical (OECD, 2002).

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

The major global industrial uses of TBP are as a flame retardant component of aircraft hydraulic fluid and as a solvent for rare earth extraction and purification from its ores (Government of Canada, 2009). These uses comprise over 80 % of the total global production (OECD, 2002).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- The Association of Southeast Asian Nations (ASEAN) Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.
- China List of Banned substances for use in Cosmetics (Chinese)
- EU Cosmetic Directive 76/768/EEC Annex II: List of Substances which must not form part of the Composition of Cosmetic Products.
- New Zealand Cosmetic Products Group Standard - Schedule 4: Components Cosmetic Products Must Not Contain - Table 1.

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous with the following risk phrases for human health in the Hazardous Substances Information System (HCIS) (Safe Work Australia):

Carcinogenicity – Category 2; H351 (Suspected of causing cancer)

Acute toxicity – Category 4; H302 (Harmful if swallowed)

Skin irritation – Category 2; H315 (Causes skin irritation)

Exposure Standards

Australian

The chemical has an exposure standard of 2.2 mg/m³ (0.2 ppm) time weighted average (TWA).

International

The following exposure standards are identified (Galleria Chemica):

An exposure limit (TWA) of 2.2–11 mg/m³ (0.2–1 ppm) in USA (Alaska, Hawaii), Canada (Yukon), Norway and Switzerland.

Health Hazard Information

Toxicokinetics

The chemical is readily absorbed via the following routes of exposure: oral, dermal, and inhalation. Following absorption in rats, 14C-labelled chemical is distributed throughout the body tissues. After 7 days, the highest concentrations were identified in the muscle, skin and adipose tissues (residual radioactivity at <1 %), and in the carcass (<1.5 %). Excretion is independent of the administration route and is predominantly via urine (50–86 %), and to a lesser extent in the faeces (4–19 %) and in the exhaled air (2–10 %). The chemical is almost 100 % metabolised, with less than 1 % of the parent chemical detected in the urine and faeces. The major urinary metabolite was identified as dibutyl phosphate (MAK, 2002; HSDB; REACHa).

Plasma concentrations of the chemical were studied in Sprague Dawley (SD) rats for 3 routes of administration (oral, dermal and intravenous) at doses of 10 or 350 mg/kg bw. Radiolabelled chemical is 100 % absorbed in rats given single and repeated oral doses. Peak plasma concentrations of 10 or 350 mg/kg bw of the chemical were reached at 90–140 minutes and 180–400 minutes, respectively. A major portion of the chemical was recovered within 48 h in the urine and faeces. The major route of elimination was via the kidneys (MAK, 2002).

In rats following dermal exposure for 6 h, 40–56 % of the chemical was absorbed and the peak plasma levels were reached after 4 h. In minipigs, the chemical was poorly absorbed (maximum 5 %) via the dermal route while 57–92 % of the applied doses could be washed off the skin. The chemical was mostly eliminated via the urine (MAK, 2002; REACHa).

The biotransformation of the radiolabelled chemical was studied in SD rats and the principal metabolic pathway identified as phase 1 metabolism (oxidation and hydrolysis). The butyl groups are first oxidised to form hydroxyl, keto and acid groups, followed by enzymatic hydrolysis to mono- and dibutyl phosphate. Phase II metabolism (glucuronidation) is considered a minor biotransformation route, where glutathione conjugates with an oxidised butyl group to form mercapturic acid derivatives in rats (MAK, 2002; REACH).

In an in vitro study using rat liver homogenate, the chemical was rapidly metabolised (within 30 minutes) by liver microsomal enzymes in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) to form dibutyl (3-hydroxybutyl) phosphate. A small amount was metabolised (11 %) in the absence of NADPH. In the second stage of this study, the incubation time was increased to 2.5 h further yielding 2 metabolites from the primary metabolite: dibutyl hydroxybutyl phosphate and butyl bis(hydroxybutyl) phosphate (MAK;2002; REACHa).

Acute Toxicity

Oral

The chemical is classified as hazardous with hazard category ‘Acute Toxicity Category 4’ and hazard statement ‘Harmful if swallowed’ (H302) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). The available data median lethal doses—LD50 values that are in the ranges of 1164 to 3350 mg/kg bw in rats and 400 to 1240 mg/kg bw in mice—support this classification (OECD, 2002; REACHa). Reported signs of toxicity included blood around the nostrils, mouth and eyes, ruffled fur, lying on the side, laboured breathing and convulsions (BG RCI, 2000; REACHa).

Dermal

The chemical was reported to have low acute toxicity via the dermal route (LD50 >3100 mg/kg bw in rabbits and >9700 mg/kg bw in guinea pigs) (OECD, 2002).

Inhalation

The acute toxicity for the chemical has not been completely established. The lowest reported median lethal concentration (LC50) in rats is >4242 mg/m^3 (4.2 mg/L) (guideline study). Other non-guideline studies have reported LC50 values > 5000 mg/m^3 (5 mg/L). The LC50 in rats for the structurally similar analogue, triethyl phosphate (CAS No. 78-40-0) is > 8817 mg/m^3 (8.8 mg/L).

In an acute toxicity study conducted according to OECD TG 403, Wistar rats (5/sex/dose) were exposed to the chemical at 511, 801, 2140 or 4242 mg/m^3 in air (aerosol) for 4 h followed by 28 days of observations. Clinical signs of toxicity included diminished motility, ataxia, adynamia in the hind paw, prostration, piloerection, untended fur, nose secretion, sniffing sounds, difficulties in breathing or abnormally slow breathing (bradypnoea), breathing sounds, blood-stained tears (chromodacryorrhea), red-coloured urine, inflated abdomen, bloody snout, loss of myotactic reflex and reduction of body weight. At the highest dose there were 2/5 male mortalities and no female mortality The LC50 is >4242 mg/m^3 (OECD, 2002).

In a non-guideline study, 3 rats (strain and sex not specified) were exposed to the chemical at 4000 or 42000 mg/m^3 air for 6 h. One mortality occurred in rats exposed at 42000 mg/m^3. At the low dose irritation was observed, but no mortality occurred. The LC50 is >42000 mg/m^3. No further information is available.

In a non-guideline study, rats (3; strain not specified) were exposed to the chemical at 1500 mg/m^3 for 6 h. No mortality occurred; however, strong respiratory irritation was observed (OECD, 2002). No further information is available.

In a non-guideline study, Wistar rats (5/sex/dose) were exposed to the chemical at 20000, 42000 or 100000 mg/m^3 for 1 h and observed for 14 days. No animals survived the 2 highest doses. All mice exposed to 20000 mg/m^3 survived. The LC50 is >20000 and < 42000 mg/m^3. According to GHS a 1 h LC50 can be converted to a 4 h value by dividing it by 4. This results in an LC50 value that is >6666 and <13333 mg/m^3 (OECD, 2002).

Analogue data (triethyl phosphate)

In an acute toxicity study conducted according to OECD TG 403, Wistar rats (5/sex/dose) were exposed to the chemical at 1400, 3360 or 8817 mg/m^3 air for 4 h. Clinical signs of toxicity included untended fur, reduced motility, miosis, bloody snout, ataxia, miosis, reduce breathing and accelerated breathing. No mortality was observed. The LC50 is >8817 mg/m^3 (8.8 mg/L) (REACHb).

Corrosion / Irritation

Skin Irritation

The chemical is classified as hazardous with hazard category ‘Skin irritation – Category 2’ and hazard statement H315 (Causes skin irritation) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). The available data support this classification.

Skin irritation studies conducted in rabbits, guinea pigs and humans (see **Observation in Humans**) show the chemical to be irritating to highly irritating, using a range of application methods to intact or abraded skin (OECD, 2002; REACHa).

Eye Irritation

The chemical is reported to be a slight eye irritant in rabbits. The data available are insufficient for supporting a hazard classification of the chemical as an eye irritant.

Three irritation studies showed the chemical to be irritating (slight or transient irritation) to the eyes of rabbit (OECD, 2002). The eye irritation scores are not available.

The chemical (100 µL) was administered into one eye of 3 rabbits (the other eye remained untreated), and washed out after 24 h with NaCl. The animals were observed for 21 days after administration of the chemical dose. The chemical was slightly irritating to the rabbit's eye (conjunctivae reddening was not fully reversible by day 14) (REACHa).

Observation in humans

Symptoms in exposed workers included nausea, headache, skin irritation, and skin rashes (OECD, 2002). One human case study with cotton swabs soaked in 10, 50, and 75 % solutions of the chemical and applied to skin occlusively for 3, 24, and 48 h, respectively resulted in irritation at the 50 and 75 % concentrations (OECD, 2002).

Sensitisation

Skin Sensitisation

The chemical is not considered to be a skin sensitiser.

In a Buehler test conducted in accordance with OECD TG 406 in Hartley guinea pigs (10/sex), induction was undertaken by applying a 10 % solution of TBP in mineral oil to shaved skin of the shoulder under occlusion 6 h weekly for 3 weeks. The challenge was carried out 14 days later using a 10 % solution of the chemical. No positive skin reactions were observed (BG RCI, 2000).

In an open epicutaneous test in guinea pigs, no skin sensitisation was observed with 10 % concentration of the chemical in mineral oil (OECD, 2002).

In a non-guideline study the chemical was considered sensitising in 6 (out of 14) guinea pigs. In this study, paper manufactured using the chemical was directly applied to the skin of the animals. No other details of the study are available (REACHa).

Observation in humans

A human patch test showed no sensitisation potential in 53 volunteers exposed to 15 applications of a <5% solution of the chemical (OECD, 2001).

Repeated Dose Toxicity

Oral

The chemical causes dose-dependent bladder effects including irritation, inflammation and epithelial hyperplasia in rats and mice . Rats are more sensitive to the effects of TBP. The chemical also induces tumours in the bladder of rats, (see **Carcinogenicity**). Chronic carcinogenicity studies and negative genotoxicity studies (see **Genotoxicity**) indicate that bladder tumours may be caused by direct cell damage leading to hyperplasia of the bladder epithelium. Therefore, the observed changes in the urinary bladder following repeated exposure to TBP can be considered as covered appropriately by the Carcinogenic category 2 classification (ECHA, 2013). The chemical is not expected to cause other serious damage to human health.

In a repeated dose toxicity study conducted in accordance with US EPA guidelines, Sprague Dawley (SD) rats (15/sex/dose) were treated with TBP in diet at 0, 8, 40, 200, 1000 or 5000 ppm for 13 weeks (equivalent to 0, 1, 3, 14, 68 or 360 mg/kg bw/day for males and 0, 1, 3, 16, 81 or 423 mg/kg bw/day for females). The treatment did not affect mortality. Body weight gain and food intake were significantly reduced and absolute and relative liver weights were increased in both sexes receiving the highest dose (360 or 423 mg/kg bw/day). Liver-related blood parameters were affected at the highest dose in both sexes; however, no histopathological abnormalities were observed in the liver. Generalised transitional cell hyperplasia was observed in the urinary bladders of all males receiving 68 or 360 mg/kg bw/day and in the majority of females receiving the highest dose (423 mg/kg bw/day). A no-observed adverse effect level (NOAEL) of 14 mg/kg bw/day was reported based urinary bladder hyperplasia in male rats treated with 68 or 360 mg/kg bw/day TBP (Government of Canada, 2009; MAK, 2002; OECD, 2002; US EPA, 2010; REACHa).

In a 10 week study focusing on bladder effects of TBP, male SD rats (10/dose) were fed TBP in diet at 0, 200, 700 or 3000 ppm (equivalent to 15, 53, or 230 mg/kg bw/day). Another group received 230 mg/kg bw/day TBP and ammonium chloride (12300 ppm in diet) to evaluate the effect of urinary acidification (ammonium chloride prevents potentially irritating precipitate formation). A final group received 230 mg/kg bw/day TBP followed by a 10 week recovery period (recovery group). Body weight gain was reduced in high dose rats but this was reversible in the recovery group. Food consumption was unaffected. Urinalysis was normal apart from a slight decrease in osmolarity and creatinine concentration in high dose rats. No treatment related crystalluria, urinary precipitate, or calculi were present in the urine even without ammonium chloride treatment. General hyperplasia and increased bromodeoxyuridine (BrdU) labelling (indicative of cell proliferation) was observed in rats receiving the two highest doses (dose-dependent). Incidences of papillary and nodular hyperplasia were significantly increased in the high dose group. Focal necrosis of the bladder epithelium with ulceration and haemorrhage into the lumen was observed in the mid and high dose groups. Inflammation associated with the ulceration was observed at the highest dose only. Acidification of the urine did not prevent epithelial hyperplasia in the bladder, but it reduced the severity of the effects at the highest dose. Bladder changes were reversible in the recovery group and no significant hyperplasia was observed after 10 weeks without treatment. Recovery group animals had increased fibrosis of the submucosa that may represent scar tissue formed during ulceration. No NOAEL was identified in this study (Government of Canada, 2009; MAK, 2002; OECD, 2002; US EPA, 2010; REACHa).

In a repeated dose toxicity study, SD rats (12/sex/dose) received 0, 143 or 238 mg/kg bw/day TBP orally by gavage 5 days a week for 18 weeks. Treatment with TBP had no adverse effects on clinical signs or haematological findings. Body weights were decreased in high dose males. Relative kidney weights, absolute and relative liver weight, and absolute spleen weight were increased in high dose females. Diffuse hyperplasia of the urinary bladder epithelium and subepithelial capillaries was observed in all treated animals. No other treatment-related gross or histopathological abnormalities were observed. No NOAEL was identified in this study (MAK, 2002; OECD, 2002; US EPA, 2010; REACHa).

In a repeated dose toxicity study conducted in accordance with US EPA guidelines, CD-1 (Swiss albino) mice (15/sex/dose) were treated with TBP in diet 0, 500, 2000 or 8000 ppm for 13 weeks (equivalent to 96, 383 or 1479 mg/kg bw/day for males and 119, 462 or 1769 mg/kg bw/day for females). Treatment with TBP had no adverse effects on mortality or clinical signs of toxicity. Body weight gain and food consumption was reduced in high dose mice. Absolute and relative liver weights were increased in both sexes receiving the mid to high doses of TBP. Centrilobular hepatocyte hypertrophy was significantly increased in mid and high dose males and high dose females. Urinary bladder epithelial hyperplasia was observed in mid and high dose animals of both sexes (dose-dependent). A NOAEL of 96 mg/kg bw/day was reported based on liver and bladder effects in males receiving TBP at the two highest doses (Government of Canada, 2009; MAK, 2002; OECD, 2002; US EPA, 2010; REACHa).

In a reproductive toxicity study (see **Reproductive toxicity**) both male and female (F0 and F1) rats showed dose-dependent urinary bladder epithelial hyperplasia at doses ≥ 53 mg/kg bw/day. Renal pelvic epithelial hyperplasia was observed in F0 and F1 males of the high dose group (225 mg/kg bw/day). Hepatic centrilobular hypertrophy was observed in F0 and F1 females of the mid (53 mg/kg bw/day) and high (225 mg/kg bw/day) dose groups (Government of Canada, 2009; MAK, 2002; OECD, 2002; US EPA, 2010; REACHa).

In a 24 month carcinogenicity study (see **Carcinogenicity**) SD rats (50/sex/dose) received TBP in diet 0, 200, 700 or 3000 (equivalent to 8.9, 32.5 or 143.3 mg/kg bw/day for males and 0, 11.6, 42.0 or 181.5 mg/kg bw/day for females). Body weight gains were significantly decreased in high dose rats. The only significant non-neoplastic finding was a dose related increase in the incidence and severity of urinary bladder hyperplasia in both sexes at the two highest doses (Government of Canada, 2009; MAK, 2002; OECD, 2002; US EPA, 2010; REACHa).

Dermal

No data are available.

Inhalation

Limited data are available.

In two inhalation studies, rats and rabbits were exposed to ~5 or 13.6 mg/m^3 TBP for 5 h/day, 5 days/week for 4 months. In both species, cholinesterase activity was decreased by 33 % at the high dose; however, activity returned to normal in the post

exposure period. There was no effect on cholinesterase activity at the low dose (OECD, 2002). No further information is available.

Genotoxicity

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

Five Ames assays gave negative results with and without metabolic activation. Three other in vitro assays (cytogenetic and mammalian cell gene mutation assays) were also negative (OECD, 2002).

Results of two in vivo genotoxicity studies confirm the negative finding of the in vitro studies. These included a rat cytogenetic assay where there was no increase in aberrant cells in bone marrow after dosing at the maximum tolerated dose of 1200 mg/kg bw via gavage and a recessive lethal mutation test in *Drosophila melanogaster* (OECD, 2002; US EPA, 2010).

Carcinogenicity

The chemical is classified as hazardous with hazard category Carcinogenicity – Category 2 and hazard statement 'Suspected of causing cancer' (H351) in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). The available data support this classification.

In a 24 month carcinogenicity study, SD rats (50/sex/dose) received TBP in diet 0, 200, 700 or 3000 (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. A dose-related increase in the incidence and severity of urinary bladder hyperplasia was also observed in male and female rats. Increased incidence 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 (Government of Canada, 2009; MAK, 2002; OECD, 2002; US EPA, 2010; REACHa).

In a 24-month carcinogenicity study, CD-1 mice received TBP in diet (150–3500 ppm) equivalent to 24, 169 or 585mg/kg bw/day for males and 29, 206 and 711mg/kg bw/day for females. The mortality rate 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 (Government of Canada, 2009; MAK, 2002; OECD, 2002; US EPA, 2010; REACHa).

Reproductive and Developmental Toxicity

Based on the available data, the chemical does not cause reproductive effects in rats (NOAEL for reproductive toxicity >225 mg/kg bw/day). Developmental toxicity was observed in a two generation rat study, but only at maternal toxic doses (NOAEL for maternal toxicity <15 mg/kg bw/day).

In a two generation reproductive toxicity study, SD rats received TBP in diet at 200, 700, or 3000 ppm (approx. 15, 53, or 225 mg/kg bw/day). There was no evidence of treatment- related reproductive organ histopathological lesions or pre or postnatal mortality at any dose. In adults, dose levels of 700 and 3000 ppm resulted in reductions in body weights, body weight gain, and food consumption during the F0 and F1 pre-breeding dosing periods. At the 200 ppm level, transient effects on body weight and food consumption in adults and reduced body weights of pups were observed. The only treatment-related postnatal effect was reduced pup weight in the high dose group, which was associated with maternal toxicity. Maternal toxicity effects are discussed in the **Repeated dose toxicity** section. Based on these effects, the reproductive toxicity NOAEL was >3000 ppm (>225 mg/kg bw/day), while the maternal toxicity NOAEL and post-natal toxicity NOAEL were both less than 200 ppm (OECD, 2002).

In three separate teratology experiments (two in rats and one in rabbits), delayed ossification, rudimentary ribs and reduced foetal weights effects were observed only at maternally toxic doses and only in rats. The NOAEL for rabbits was the highest dose tested (400 mg/kg bw/day). The NOAEL for foetal effects in rats was 750 mg/kg bw/day and the NOAEL for maternal toxicity was 62.5 mg/kg bw/day (OECD, 2002).

Other Health Effects

Neurotoxicity

The neurotoxicity of the chemical has been studied in several species including the rat, hen, and rabbit. In these studies, the chemical produced either no signs of neurotoxicity or only slight or transient effects on measured endpoints. Effects on acetyl cholinesterase were minor, only occurred at high doses or were reversible.

In a 13 week neurotoxicity test in SD rats (daily doses as high as 325 mg/kg bw/day), neurotoxicity effects were not seen. The treatment did not alter behaviour, adversely affect motor activity, or result in neurohistopathological changes. In general, no treatment related effects were seen. A NOAEL was not reported (OECD, 2002; ECHA 2011).

In Wistar rats, feeding at 5000 or 10000 mg/kg diet (equivalent to 375 or 750 mg/kg bw) for 10 weeks resulted in higher brain cholinesterase activity in the treated groups compared with the control group (quantitative data not available). However, no changes of cholinesterase activity in the liver and serum were reported. Decreased absolute brain weight in the high dose group was noted (OECD, 2002).

In an 18 week oral gavage study (see **Repeated dose toxicity: Oral**) high-dose (238 mg/kg bw/day) females had significantly decreased red blood cell acetylcholinesterase activity (8 % below controls) (US EPA, 2010).

In a repeated dose inhalation toxicity study (see **Repeated dose toxicity: Inhalation)** a reversible 33 % reduction in cholinesterase activity was reported in rats and rabbits exposed to the chemical at 13.6 mg/m^3 for 4 months. In animals exposed to a low dose (~5 mg/m^3) no effects on cholinesterase activity were observed (OECD, 2002).

In a delayed neurotoxicity tests in hens, in which the chemical was administered either in a single high dose (1500 mg/kg bw) or in two high doses (1500 mg/kg bw each) 21 days apart, there was no relevant inhibition of brain acetylcholinesterase. The hen is considered the most sensitive species for identifying neurotoxins that cause delayed peripheral neuropathy (OECD, 2002; REACHa).

Risk Characterisation

Critical Health Effects

The main critical effect to human health is carcinogenicity. The chemical can cause skin irritation and harmful effects if ingested.

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. In 2001, the OECD SIAR stated that no consumer products containing the chemical are available. The chemical is only listed once (for use in brake fluid at 2 %) in the US Household Products Database.

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. The chemical has been detected in house dust and in indoor air at low levels (Kanazawa et al., 2010). The government of Canada estimated the margin of exposure to be 37500 based on estimated intake of TBP from indoor air and food. This MOE can be considered adequately protective of human health. MOE values for the use of certain products such as paints and brake fluid were lower (500–15000); however, the frequency of use of these products (1–2 times per year) is low. Therefore, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During product formulation, oral, dermal 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 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.

Based on the available data, the hazard classification in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety, and poisons legislation as adopted by the relevant state or territory. No further assessment is required.

Regulatory Control

Public Health

Considering the available information to indicate low public exposure from this chemical no regulatory controls are recommended. However, if new information becomes available, NICNAS will consider recommending risk management for public safety.

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]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Not Applicable	Causes skin irritation - Cat. 2 (H315)
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 to minimise the risk from dermal, oral 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 storage, handling and use of a hazardous chemical are dependent 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:

- use of closed systems or isolation of operations;
- use of 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;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimisation of manual processes and work tasks through automation of processes;
- work procedures that minimise splashes and spills;
- regular cleaning of equipment and work areas; and
- use of 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 be relied upon on its own to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selection of 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 hazardous chemical are prepared; and
- management of risks arising from storage, handling and use of 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 physical hazards of the chemical has not been undertaken as part of this assessment.

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