Butylated triaryl phosphate esters: Human health tier II assessment

29 June 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phosphoric acid, 4-(1,1-dimethylethyl)phenyl diphenyl ester	981-40-8
Phosphoric acid, (1,1-dimethylethyl)phenyl diphenyl ester	56803-37-3
Phosphoric acid, bis [(1,1,dimethylethyl) phenyl] phenyl ester	65652-41-7
Phenol, isobutylenated, phosphate (3:1)	68937-40-6

Preface

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

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

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

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS

already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

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

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

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

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The substances in this assessment are triaryl phosphate esters with tert-butyl or isobutyl groups present in one (CAS Nos 56803-37-8 and 981-40-8), two (CAS No. 65652-41-7) or all (CAS No. 68937-40-6) of the phenol moieties. All substances apart from CAS No. 981-40-8 are Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB) substances containing various different constituents. The UVCB butylated triaryl phosphate esters can have butyl substituents at ortho, meta or para positions on one, two or three of the phenyl rings. Thus, the number of potential isomers is large. The isobutyl and the tert-butyl substituted triaryl phosphate esters are expected have similar toxicity profiles. In this assessment, the group butylated triaryl phosphate esters refers to isobutyl and tert-butyl triaryl phosphate esters with an unspecified number of butyl groups.

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 Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US Environmental Protection Agency (EPA) Flame retardants assessment update (US EPA, 2015); Environmental and health screening profiles of phosphorous flame retardants (Danish EPA, 2016); the US Household Products Database (US HPD); the US National Toxicology Program (NTP); Toxicological Profile for Hydraulic Fluid (ATSDR, 1997); United States Environmental Protection Agency (US EPA) Chemical and Product Categories (CPCat) database; and United Kingdom (UK) Environment Agency report (2009).

tert-Butylphenyl diphenyl phosphate (CAS No. 56803-37-3) has reported cosmetic use as plasticiser in nail polish (NTP), but it is not reported as cosmetic ingredient in European Commission cosmetic ingredients database (CosIng) or in US Personal Care Products Council cosmetic ingredient database (INCI Dictionary).

The substances may have domestic uses, including in lubricants, greases, adhesives and sealants. Di-tert-butylphenyl phenyl phosphate (CAS No. 65652-41-7) has reported domestic use in several auto products up to a concentration of 7 % (US HPD).

Butylated triaryl phosphate esters are reported to be widely used for both flame retardant and lubricating properties. Butylated triaryl phosphate esters may have commercial and site-limited uses, including in manufacture of flame retarded fluids, plastics and textiles, including polyurethane foams, high performance hydraulic fluids, lubricants, and metal working fluids.

The substances may be found in household products as flame retardants. Products may include textiles, furniture and electrical equipment.

Restrictions

Australian

No known restrictions have been identified.

International

In Maine, United States of America (USA) – Legislature is being implemented to restrict a flame retardant chemical or mixture that includes flame retardant chemicals to 0.1 % in new residential upholstered furniture containing fabrics, other coverings or cushioning materials. The restriction takes effect in 2019 (Maine Legislature, 2017). Similar restrictions are considered in San Francisco (USA; Environment Code, 2017).

Existing Worker Health and Safety Controls

Hazard Classification

The 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

The majority of data are available for commercial butylated triaryl phosphate ester formulations including Phospflex 51B, H-19457, Santicizer 154, Durad 22B, Fyrquel 220 and Fyrquel 150. Commercial butylated triaryl phosphate ester formulations may include mono-, di-, and tri-substitutions at various positions and may contain other compounds such as triphenyl phosphate (TPHP; CAS No. 115-86-6) depending on the manufacturing, purification and processing of the substance (US EPA, 2015). A description of the components or isomer content is included in the assessment when available.

Toxicokinetics

Based on the limited data available and data for other triaryl phosphate esters, the butylated triaryl phosphate esters are expected to have some absorption by all routes of exposure.

The dermal and oral absorption of a commercial butylated triaryl phosphate ester formulation was investigated in female F-344 rats. The test substance was detected in several tissues 1 hour after exposure with levels peaking at 24 hours. Liver concentrations were much higher following oral adminstration. Kidney, ovary, and adrenal concentrations were much higher relative to other organs following dermal exposure compared to oral exposure (Kinead at al. 1991).

Following dermal administration to guinea pigs, tert-butylphenyl diphenyl phosphate (CAS No 56803-37-3) was not readily absorbed through the skin (US EPA, 2015).

Highly specific metabolic pathways exist for certain aryl phosphate esters:

1. The ortho-methyl phenyl (cresyl) isomers can be oxidised to the hydroxymethyl derivative, to an aldehyde and the a carboxylic acid followed by conversion to the neurotoxic cyclic phenyl saligenin phosphate (NICNASa). However, the increasing size (number of carbon atoms) of the substituent, as in the assessed substances, interferes with the metabolic activation steps reducing the potential to produce neurotoxic metabolites (Weiner and Jortner, 1999).

2. The para-ethyl phenyl isomers can be hydroxylated to give alpha-hydroxyethyl group, which is then transformed to an acetyl group resulting with potentially neurotoxic metabolites (Eto et al., 1971). This pathway has not been observed for the chemicals in this assessment (see ***Neurotoxicity*** section).

Acute Toxicity

Oral

Based on results from various animal tests following oral exposure to butylated triaryl phosphate esters, the substances have low acute toxicity. Studies in rabbits and rats orally treated with butylated triaryl phosphate esters have reported median lethal dose (LD50) levels of >2000 mg/kg bw (Johannsen et al., 1977; US EPA, 2015; Galleria Chemica; REACHa).

Adverse clinical signs in rats included mild to moderate depression, piloerection, reddish stained muzzles, lacrimation, chromodacryorrhoea, diarrhoea, and yellowish-brown anogenital stains (REACHa).

Dermal

Based on results from acute dermal toxicity studies with butylated triaryl phosphate esters, the substances have low acute dermal toxicity. The LD50 for butylated triaryl phosphate esters in rats and rabbits is >2000 mg/kg bw (US EPA, 2015; Galleria Chemica; REACHa).

Inhalation

Based on the acute inhalation toxicity studies with tert-butylphenyl diphenyl phosphate (CAS No. 56803-37-3) and a commercial butylated triaryl phosphate ester formulations, the substances are not expected to be acutely toxic if inhaled.

In an acute inhalation toxicity study, a rat inhalation median lethal concentration (LC50) value of >200 mg/L was reported for tert-butylphenyl diphenyl phosphate (CAS No. 56803-37-3) (US EPA, 2015).

In an acute inhalation toxicity study, a rat inhalation LC50 value of >3.1 mg/L (highest concentration tested) was reported for a commercial product composed of 75–80 % of tertbutylphenyl diphenyl phosphate (CAS No. 56803-37-3) and 20–25 % of TPHP (CAS No. 115-86-6) (US EPA, 2015).

No systemic effects were observed in rats exposed to a commercial butylated triaryl ester at concentration of 6310 mg/m^3 for 4 hours (ATSDR, 1997).

Corrosion / Irritation

Skin Irritation

Based on a number of acute dermal irritation tests with butylated triaryl phosphate ester formulations, the substances are expected to be at most slightly irritating to the skin. The effects are not sufficient to warrant hazard classification.

In an Organisation for Economic Cooperation and Development (OECD) Test Guideline (TG) 404 study, very slight or well-defined erythema was reported in rabbits dermally exposed to tert-butylphenyl diphenyl phosphate (CAS No. 56803-37-3). The effects persisted through to day 10 after exposure (US EPA, 2015)

In a US EPA guideline skin irritation study, 6 Stauffland albino rabbits were treated with 0.5 mL of the commercial butyl triaryl phosphate ester formulation under a gauze patch for 24 hours. The formulation produced mild erythema (4 rabbits) and mild oedema (1 rabbit) on intact and abraded skin. At the 72 hours after application, irritation was reduced with mild erythema reported in one of the six rabbits (REACHa).

In a non-guideline skin irritation study, 6 New Zealand White (NZW) rabbits were treated with 0.5 mL of commercial butylated triaryl phosphate ester formulation for a 24 hours. Mild erythema was noted at the 24 hour observation period in two of the six animals. All effects were reversible by 72 hours (UK Environment Agency, 2009; REACHa).

Eye Irritation

Based on a number of acute eye irritation tests with butylated triaryl phosphate ester formulations, the substances are expected to be at most slightly irritating to the eyes (US EPA, 2015; REACHa). The effects are not sufficient to warrant hazard classification.

In four separate eye irritation tests comparable to OECD TG 405, 9 Stauffland or NZW albino rabbits were applied a single instillation of 0.1 mL of three different commercial butylated triaryl phosphate ester formulations (neat) into one eye (separate experiments for each formulation). The treated eye was washed with water 20-30 seconds after exposure in 3 rabbits and the eyes were left unwashed in the remaining 6 rabbits. The untreated eye of each animal served as a negative control. No irritation was reported in the washed and unwashed eyes of rabbits following exposure to three of the formulations (REACHa). For the other formulations, mild redness of the conjunctivae was observed in two rabbits (both washed and unwashed eyes) with all effects reversed by 72 hours after treatment (UK Environment Agency, 2009).

Sensitisation

Skin Sensitisation

A commercial butylated triaryl phosphate ester formulation was not sensitising in humans (see ***Observation in Humans*** section), while ambiguous sensitisation potential was reported in a local lymph node assay (LLNA). Based on the weight of evidence of human data, data for other aryl phosphate esters, negative Quantitative Structure Activity Relationship (QSAR) predictions for skin sensitisation and lack of structural alerts for protein binding (molecular initiating event for skin sensitisation), the substances are not expected to be potent skin sensitisers.

In a LLNA conducted according to OECD TG)429, CBA/ Ca mice were exposed to a butylated triaryl phosphate ester formulation in acetone/olive oil (4:1 v/v) at 25, 50 or 100 % w/v by topical application on the dorsal surface of ear. Stimulation indices (SI) for 25 %, 50 % and 100 % of the formulation were reported as 3.36, 4.00, and 3.24, respectively. No dose response relationship was observed (REACHa).

The iso-butylated or the tert-butylated phosphate esters were not predicted to be skin sensitisers (>80 % in domain; OASIS TIMES v2.27.19) or protein binders (QSAR Toolbox v. 3.4) in the in silico tests. In addition, other aryl phosphate esters are not expected to be skin sensitisers (NICNASa; NICNASb; NICNASc; NICNASd; NICNASe).

Observation in humans

In a well performed repeated insult patch test in 50 men and women, a commercial butylated triaryl phosphate ester formulation (up to 10 %) was not allergenic to any of the subjects (REACHa).

Additionally, there have been no incidences (known to the management) of sensitisation in workers related to the use and production of isobutylated triphenyl phosphate (CAS No. 68937-40-6) at a facility in the USA. This includes years of experience with the substance in various products on the production facility in Gallipolis Ferry, WV, USA (REACHa).

Repeated Dose Toxicity

Oral

Systemic effects in the reproductive organs and adrenals are common with substituted aryl phosphate esters (NICNASa; NICNASc; NICNASd; NICNASe). Whilst effects in the ovaries and adrenals were observed in some studies, these generally were observed at high doses or effects were not severe enough to warrant hazard classification.

In a 90-day oral repeat dose toxicity study similar to OECD TG 408, Sprague-Dawley (SD) rats (20 animals/sex/dose) received a commercial butylated triaryl phosphate ester formulation (78–80 % *tert*-butylphenyl diphenyl phosphate—CAS No. 56803-37-3 and 20–25 % TPHP—CAS No. 115-86-6) in concentrations of 0, 100, 400 and 1600 ppm by diet (6.6, 26.7 and 107.5 mg/kg/day, respectively for males and 7.7, 30.0, and 124.8 mg/kg/day, respectively for females). No treatment related mortality or clinical signs were reported. The liver and adrenal (females only) weights were significantly increased in the high dose groups. No corresponding histopathological changes were observed. The effects on adrenal weights in females were dose dependent. The statistically significant differences in haematology and clinical chemistry values and in red blood cell, plasma and brain cholinesterase activities between control and treated animals were minimal or inconsistent. Based on the adrenal effects, a NOAEL of approximately 30 mg/kg bw/day (equivalent to 400 ppm) was established for female rats. Due to lack of effects on haematology and clinical chemistry, the liver effects were considered adaptive (UK Environment Agency, 2009; US EPA, 2015; REACHa).

Rats were treated via oral gavage with 1700 mg/kg/day of a butylated triphenyl phosphate fluid, in either a sesame oil vehicle or neat, for 20, 40, or 60 days. Enlargement of the adrenals and lipidosis and cytoplasmic vacuolization of the adrenal cortex and ovarian interstitial cells were observed (ASTDR, 1997; US EPA 2015). In addition, rats treated with 1900 mg/kg/day butylated triphenyl phosphate for 40 days by gavage were reported to show hypertrophy and vacuolization of ovarian interstitial cells (ASTDR, 1997).

In several 90-day dietary studies with CAS No. 56803-37-3 in rats, no treatment related effects were reported. In each study, the NOAEL was established as the highest dose tested (up to 530 mg/kg bw/day (US EPA, 2015)). In another 90-day repeat dose toxicity study similar to OECD TG 408, rats (15 animals/dose/sex) received *tert*-butylphenyl diphenyl phosphate (CAS No. not specified) in concentrations of 0, 100, 300 and 1000 ppm by diet. No treatment related mortality or clinical signs were reported. No effects were reported in the brain, gonads, heart, kidneys, liver and spleen. No information was reported concerning the

adrenals. A NOAEL of 1000 ppm (equivalent to approximately 72 and 86 mg/kg bw/day) was established for male and female rats, respectively (REACHa).

Dermal

Repeated dermal exposure to a commercial butylated triaryl ester significantly reduced plasma and brain cholinesterase activity in rabbits. However, the effect on cholinesterase activity was not shown to cause neurotoxicity (cholinergic stimulation; see ***Neurotoxicity*** section). Effects in the adrenals and ovaries were only observed at high doses. Hazard classification is not considered warranted.

In a dermal repeat dose toxicity study similar to OECD TG 410, a commercial butylated triaryl phosphate ester formulation (43.2% tertbutylphenyl diphenyl phosphate—CAS No. 56803-37-3, 40.2% TPHP—CAS No 115-86-6, 14% di-*tert*-butylphenyl phenyl phosphate—CAS No. 2528-36-1 and 2% tri-*tert*-butyl phenyl phosphate—CAS No. 78-33-1) at dose levels of 10, 100 and 1000 mg/kg bw/day was applied to the skin of NZW rabbits (10 animals/dose/sex), 5 days a week for 3 weeks. Control rabbits were treated with distilled water. No treatment related mortality was reported. Higher incidences of oedema, atonia, desquamation and fissuring were observed on the skin of the treated males and females when compared to controls. No effects on organ weights or histopathology were reported. Mean terminal plasma cholinesterase activities were significantly and dose-dependently depressed in mid and high-dose males and females when compared to controls. Mean terminal brain cholinesterase activities were significantly inhibited in most of the animals in 100 mg/kg bw/day and in all of the rabbits at the highest dose. No NOAEL was established in this study (US EPA 2015; REACHa).

In a non-guideline 6 week dermal toxicity study, a commercial butylated triaryl phosphate ester formulation (52.6% *tert*-butylphenyl diphenyl phosphate—CAS No. 56803-37-3, 30.2% bis(p-*tert*-butylphenyl) phenyl phosphate and 13.2% TPHP—CAS No. 115-86-6) was applied at a dose of 1.68 g/kg bw/day to intact skin of the clipped backs of 15 SD rats. Increased liver, kidney and adrenal weights were reported. These were accompanied by hepatocytomegaly and tubular alterations. Lipidosis was observed in the adrenals and ovaries, but this was also observed in the control animals (Kinkead at al. 1991).

Inhalation

Adverse effects consistent with other substituted aryl phosphate esters (NICNASd) have been observed in some studies. Hazard classification for repeated inhalation toxicity is recommended for the substances (see ***Recommendation*** section).

In a 90-day inhalation toxicity study similar to OECD TG 413, Charles River rats (15 animals/dose) were exposed to the aerosols of commercial butylated triaryl phosphate ester formulation by whole body inhalation at 10 mg/m^3 or 100 mg/m^3 for 6 hours per day, 5 days a week. No treatment related effects were reported in the study. A no observed adverse effect concentration (NOAEC) was reported as 100 mg/m^3/6 hr (REACH).

In an inhalation study with another commercial butylated triaryl phosphate ester, kyphosis (excessive outward curvature of the spine causing hunching of the back) was reported in rats continuously exposure to 100 mg/m^3 for 90 days. No effects in the adrenals or reproductive organs were observed. The NOAEL for kyphosis was 10.1 mg/m^3. No adverse effects were observed in rabbits exposed to 100 mg/m^3 of the same formulation continuously for 90 days (ATSDR, 1997).

However, lesions in the adrenals and ovaries were reported in another 90 day inhalation study in rats following exposure to 100 mg/m^3 for 6 hours a day, of a commercial butylated triaryl phosphate ester. Further study details are not available (US EPA, 2015).

Genotoxicity

Based on the available in vitro genotoxicity studies mainly on commercial butylated triaryl phosphate ester formulations, the substances are not considered to be genotoxic. Several in vitro (Ames tests, DNA damage and repair assays, gene mutation assays, chromosome aberration test and mammalian cell transformation assay) tests for gene mutation and clastogenicity were negative (US EPA, 2015).

Two Ames tests in five strains of *Salmonella typhimurium* (similar to OECD TG 471) and one test in *Saccharomyces cerevisiae* D4 gave negative results, both in the presence and absence of metabolic activation (CAS No. 56803-37-3 or commercial formulation containing 78–80 % *tert*-butylphenyl diphenyl phosphate CAS N.o 56803-37-3 and 20–25 % TPHP CAS No 115-86-6) (US EPA, 2015; REACHa).

A commercial formulation containing 78–80 % *tert*-butylphenyl diphenyl phosphate CAS No 56803-37-3 and 20-25 % TPHP CAS No 115-86-6 (US EPA, 2015; REACHa) gave negative results for

- chromosomal aberrations in cultured mouse lymphoma L5178Y/TK+/- cells with or without metabolic activation (REACHa);
- forward gene mutations in cultured mouse lymphoma L5178Y/TK+/- cells with or without metabolic activation; and
- sister chromatid exchanges in mouse lymphoma L5178Y/TK+/- cells with or without metabolic activation.

Carcinogenicity

Data are not available to draw conclusions regarding the carcinogenicity of the substances (US EPA, 2015). The methyl substituted aryl phosphate ester, tricresylphosphate, was not considered to be carcinogenic based on two studies undertaken in rats and mice (NICNASa).

Reproductive and Developmental Toxicity

Adverse effects on fertility including reduced litter size and histopathological changes in the testes and ovaries have been observed with other substituted aryl phosphate esters (NICNASa; NICNASc; NICNASd; NICNASe). However, for butylated triaryl phosphate ester formulations, effects on litter size and ovaries have only been observed in some studies at high doses (above 1000 mg/kg bw/day) or in non-guideline studies. Overall classification is not considered warranted.

In a reproductive toxicity study conducted according to OECD TG 421, SD rats (12 animals/sex/dose) were orally treated (gavage) with 50, 250, 1000 mg/kg bw/day of a commercial butylated triaryl phosphate ester formulation. Males were treated for total of 35 consecutive days and females for approximately 58 days, starting at 14 days prior to mating. No mortality or treatment related parental toxicity signs were reported. No effects were reported on body weights, reproductive performance or reproductive organ weights or histopathology. Mean litter size and mean number of live pups and litter weights were comparable between the treatment groups. A NOAEL of 1000 mg/kg bw/day was reported for both parental and reproductive and developmental toxicity (UK EPA 2009; REACHa).

In a reproductive study not conducted to Good Laboratory Practice (GLP), groups of F344 rat breeding pairs were orally treated (gavage) with 600, 1000 or 1700 mg/kg bw/day of a commercial butylated triaryl phosphate ester formulation (84% p-*tert*-butylphenyl phenyl phosphates—CASRN 220352-35-2 and 13 % TPHP—CAS No 115-86-6) for up to 135 days. Significantly decreased fertility index and number of live litters, prolonged oestrus cycle, and decreased mating index were observed in mid and high-dose females. There were no adverse effects on testicular or epididymal weights (UK EPA 2009; US EPA 2015). Prolonged oestrus cycles were also reported in female rats treated with a commercial butylated triaryl phosphate ester formulation at a dose of 1700 mg kg/bw/day for 20, 40 and 60 days (US EPA, 2015).

Histopathological changes in the testes were not observed in repeated dose toxicity studies (see ***Repeated dose toxicity*** section).

In a prenatal developmental toxicity study similar to OECD Guideline 414, Charles River rats were orally treated with a commercial butylated triaryl phosphate ester formulation (43.2% *tert*-butylphenyl diphenyl phosphate—CAS No. 56803-37-3, 40.2% TPHP—CAS No. 115-86-6, 14% di-*tert*-butylphenyl phenyl phosphate—CASRN 2528-36-1 and 2% tri-*tert*-butyl phenyl phosphate—CAS No. 78-33-1) at 300, 1000 and 3000 mg/kg bw/day from gestation day (GD) 6 to GD19. No significant treatment related effects were reported. A NOAEL of 3000 mg/kg bw/day was established for both developmental and maternal toxicity (US EPA, 2015; REACHa). The same formulation was tested in CD rats at doses of 250, 500, 1000, 2500 and 5000 mg/kg bw/day from GD 6 to 19. Decreases in viable foetuses and increases in post-implantation loss were only observed at the highest dose in the presence of maternal toxicity (US EPA, 2015)

In another study pregnant rats were orally treated with a commercial butylated triaryl phosphate ester formulation (75–80% *tert*-butylphenyl diphenyl phosphate—CAS No. 56803-37-3 and 25% TPHP—CAS No. 115-86-6) at 100, 400 and 1000 mg/kg

bw/day from GD6 to GD20. There were no effects on litter size (US EPA, 2015).

Other Health Effects

Neurotoxicity

Some triaryl phosphates cause organophosphate induced delayed neuropathy (OPIDN), a neurodegenerative disorder characterised by a delayed onset of prolonged ataxia and upper motor neuron spasticity. Except for tri-para-ethyl phosphate (e.g. CAS No. 3820-69-7), the neurotoxic triaryl phosphates have at least one ortho-alkylphenyl ester group (NICNASe). The ortho-alkylphenyl phosphate esters can be metabolised into neurotoxic metabolites. However, due to interference with the metabolic activation, the delayed neurotoxicity decreases as the substituent in the ortho-position becomes larger and more branched (see **Toxicokinetics**; Sjogren et al., 2010).

The butylated triaryl phosphate esters in this assessment are not potent neurotoxins. Based on the available data for the butylated triaryl phosphate esters and their commercial formulations, the substances in general do not cause neurotoxicity. Whilst no information was available to evaluate the isomer-specific neurotoxicity potential of the substances, especially the ortho-isomer, the absence of neurotoxicity is consitent with the absence of at least one hydrogen atom on the alpha carbon for the tert-butyl substituted substances. Isobutylenated substituted phenol phosphates would be expected to have greater potential for neurotoxicity compared with tert-butylated substances. No data were available for CAS No. 68937-40-6. Based on data for isopropylated phosphate esters (NICNASd) the unsymmetrical mono-ortho isomer constituent could have potential to cause neurotoxicity at high doses.

Commercial formulations

In an oral acute limit test according to the US EPA guideline (similar to OECD TG 418), the acute delayed neurotoxicity of a commercial butylated triaryl phosphate ester formulation (75–80 % tertbutylphenyl diphenyl phosphate—CAS No 56803-37-3 and 25 % TPHP—CAS No 115-86-6) was evaluated in 15 adult hens. Hens were treated with 11.7 g/kg bw of a commercial formulation administered on days 1 and 22. The positive controls (12 hens) were orally treated with 500 mg/kg bw of tri-*ortho*-cresylphosphate (TOCP; CAS No 78-30-8) in corn oil on days 1 and 22. Hens were observed for six weeks. No treatment related effects were observed in hens treated with the commercial butylated triaryl phosphate ester formulation. The TOCP treated hens showed signs of delayed motor impairment or central /peripheral axonal degeneration. In a related study measuring plasma cholinesterase (ChE) and brain neurotoxic esterase (NTE) activity, four hens were given a single dose by oral gavage of 11.7 g/kg bw. Plasma ChE activity was 56 % lower compared to vehicle controls but there was no effect on NTE activity (UK Environment Agency, 2009; REACHa).

A commercial butylated triaryl phosphate ester formulation was tested in hens at a limit dose of 2000 mg/kg bw with TOCP as positive control at 500 mg/kg bw. The commercial butylated triaryl phosphate ester formulation did not produce any signs of clinical neurotoxicity, lesions of the nervous system or brain neurotoxic esterase (NTE) inhibition. These effects were observed in TOCP treated positive controls (Weiner and Jortner, 1999).

In a subchronic study, hens (17–20 animals/dose) were orally (gavage) treated for 13 weeks with a commercial butylated triaryl phosphate in lubricating oil at a limit dose of 1000 mg/kg bw, 5 days a week for 13 weeks. No evidence of neurotoxicity was noted by assessment of brain and spinal cord NTE activity, clinical ataxia and nervous system lesions. A positive control group received 7.5 mg/kg bw of TOCP, 5 days a week for 13 weeks with an additional dose of 500 mg/kg, 12 days prior to the end of the study. The positive control hens showed neurotoxicity (REACHa).

In another acute neurotoxicity study, 3–4 white leghorn hens were treated with 12.33 g/kg bw of a commercial butylated triaryl ester formulation. Positive control hens (4 hens) received 200 mg/kg bw of TOCP. Neurotoxicity signs were evaluated 24 hours after exposure. The commercial butylated triaryl ester formulation significantly inhibited plasma cholinesterase by 62.9% when compared to controls, but had no effect on brain NTE activity. No signs of neurotoxicity (cholinergic stimulation) were reported immediately after dosing or during a 24 to 26 days observation period. The TOCP treated hens had significantly reduced plasma cholinesterase and NTE activity (REACHa).

A commercial butylated triaryl ester was reported to produce distinct clinical signs of OPIDN in chickens after 5-day administrations of 5000 mg/kg/day. However another commercial formulation (Fyrquel 150) produced effects at 240 mg/kg/day.

Fyrquel 150 has also been reported to cause neurotoxic effects in cows. Information on the composition and impurities are not known (ATSDR, 1997).

Isomer specific neurotoxicity

In a non-guideline neurotoxicity study, 9 hens were treated with para-*tert*-butylphenyl diphenyl phosphate (CAS No. not specified) at 10 g/kg bw, twice a day for 6 days (cumulative dose of 120 g/kg). No neurotoxicity (behaviour and histology) was reported in hens (Johannsen et al., 1977).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects, particularly following inhalation exposure. Neurotoxicity at high doses particularly for the isobutylenated phenol phosphate (CAS No. 68937-40-6) cannot be ruled out at high doses.

Public Risk Characterisation

The uses of the substances as a direct ingredient in cosmetic or domestic products in Australia are not known. However based on overseas information widespread use is not expected.

The substances are used internationally in the manufacture of consumer products (e.g. home furnishings) and as plasticisers in polymers. Although it is expected that the substances will be bound within the articles or coated surfaces, consumers may be directly exposed to these substances when released from articles through, for example, abrasion or dissolution (ATSDR, 2012). The butylated triaryl phosphate esters have been detected in a house dust reference material (Phillips et al., 2017). There is a lack of data on the use of the substances in consumer products in Australia and on the release of the chemical from consumer products, which does not allow a realistic exposure assessment.

The available data indicate that, although public exposure will be widespread via inhalation and dermal routes, it is at a very low level and the risk of adults and children being exposed to levels of the butylated triaryl phosphate esters, leading to adverse health effects is very low. Information is available suggesting that the use of flame retardant formulations containing butylated triaryl phosphate esters may be increasing (Phillips et al., 2017). Should further information to better characterise exposure become available, further assessment may be required.

Occupational Risk Characterisation

During product formulation, dermal, ocular and inhalation exposure may 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 substances at lower concentrations could also occur while using formulated products containing butylated triaryl phosphate esters. 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 substances could pose an unreasonable risk to workers unless adequate control measures to minimise inhalation exposure are implemented. The substances 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 HCIS (Safe Work Australia) (see ***Recommendation*** section).

NICNAS Recommendation

Assessment of the substances 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. No further assessment is required unless new information regarding the uses of the substances in cosmetic or domestic products/scenarios or information to characterise public exposure from its use in articles in Australia becomes available.

Regulatory Control

Work Health and Safety

The substances are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure through inhalation - Cat. 2 (H373)

[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 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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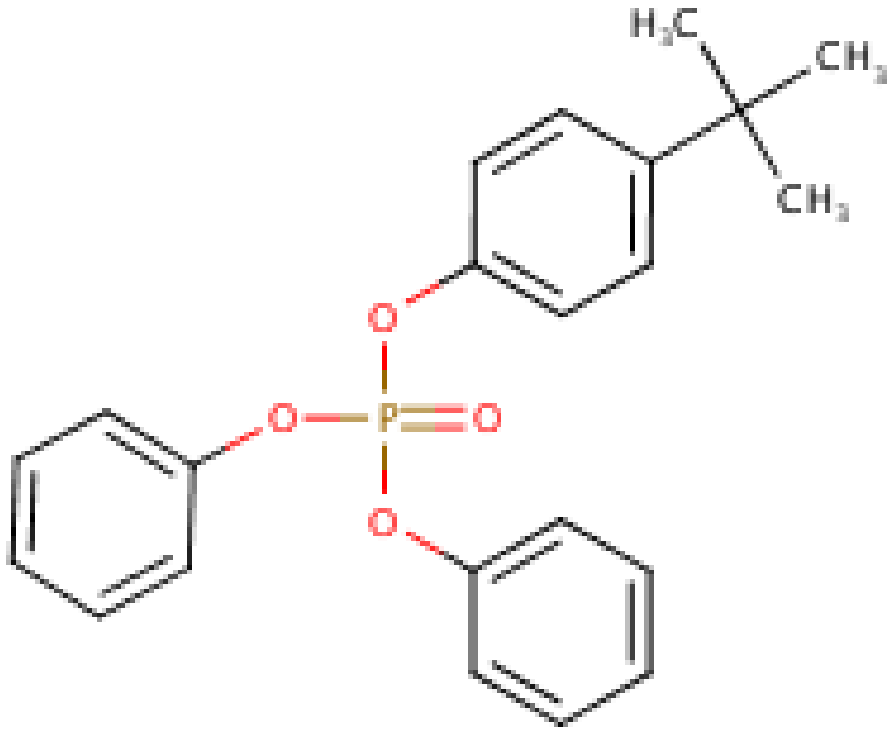
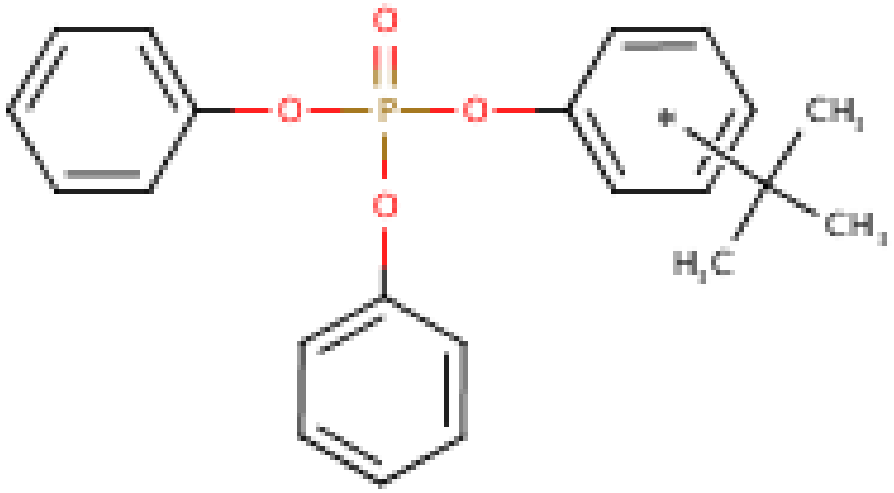
Last Update 29 June 2018

Chemical Identities

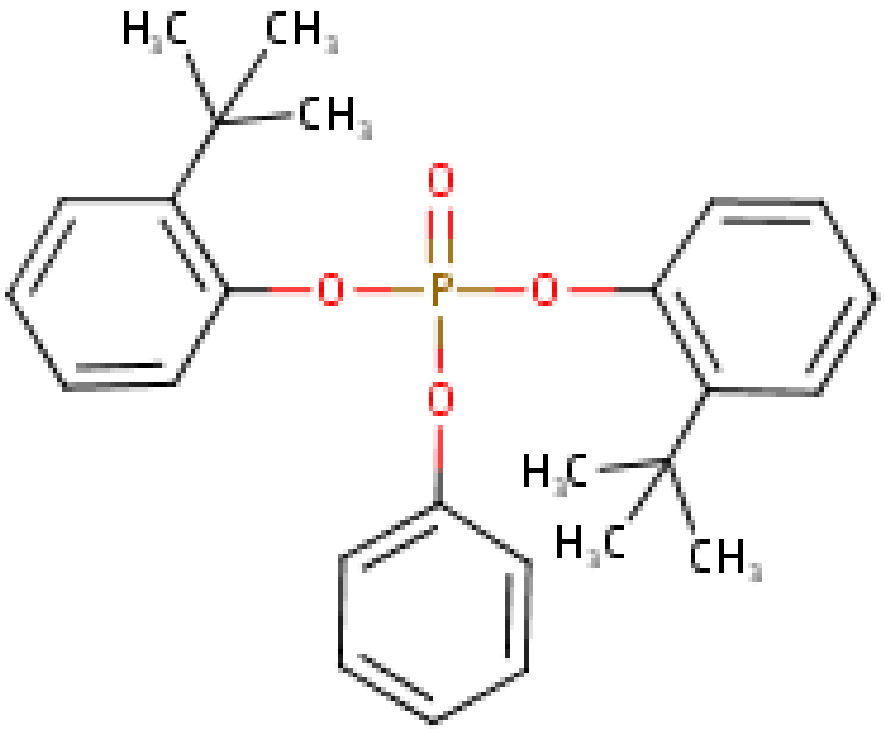
Chemical Name in the Inventory and Synonyms	**Phosphoric acid, 4-(1,1-dimethylethyl)phenyl diphenyl ester** diphenyl 4-tert-butylphenyl phosphate diphenyl p-tert-butylphenyl phosphate phosphoric acid, p-tert-butylphenyl diphenyl ester p-tert-butylphenyl diphenyl phosphate
CAS Number	981-40-8

Structural Formula	
Molecular Formula	C22H23O4P
Molecular Weight	382.40

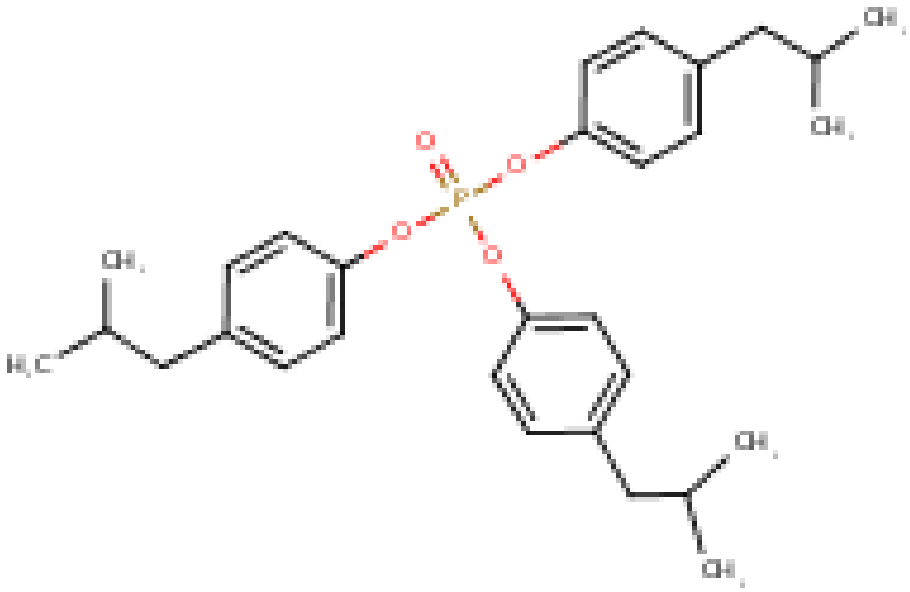
Chemical Name in the Inventory and Synonyms	**Phosphoric acid, (1,1-dimethylethyl)phenyl diphenyl ester** tert-butylphenyl diphenyl phosphate diphenyl tert-butylphenyl phosphate BPDP
CAS Number	56803-37-3
Structural Formula	

	
Molecular Formula	C22H23O4P
Molecular Weight	383.40

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, bis [(1,1,dimethylethyl) phenyl] phenyl ester** di-tert-butylphenyl phenyl phosphate bis(tert-butylphenyl)phenyl phosphate
CAS Number	65652-41-7
Structural Formula	

	
Molecular Formula	C26H31O4P
Molecular Weight	438.50

Chemical Name in the Inventory and Synonyms	**Phenol, isobutylenated, phosphate (3:1)** isobutylated triphenyl phosphate
CAS Number	68937-40-6
Structural Formula	

	
Molecular Formula	Unspecified
Molecular Weight	494.60

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