Phosphoric acid, triphenyl ester: Human health tier II assessment

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CAS Number: 115-86-6

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.

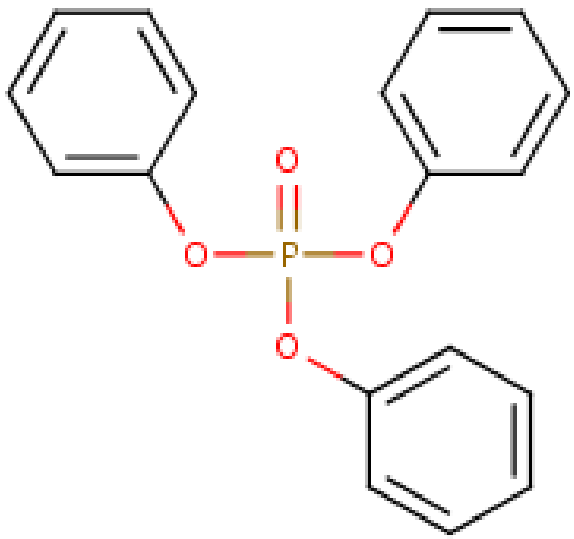
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	TPHP TPP triphenyl phosphate phenyl phosphate Celluflex TPP
Structural Formula	
Molecular Formula	C18H15O4P
Molecular Weight (g/mol)	226.282
Appearance and Odour (where available)	Colourless crystalline solid with an aromatic, phenol-like odour
SMILES	c1(OP(=O)(Oc2ccccc2)Oc2ccccc2)ccccc1

Import, Manufacture and Use

Australian

The following Australian uses have been identified through websites and safety data sheets (SDSs) available in Australia:

The chemical may have cosmetic uses in nail polishes and enamels.

The chemical may have domestic uses as a flame retardant and/or plasticiser in indoor and outdoor sealants.

The chemical may have commercial uses:

- in plastic products;
- in construction materials;
- in cellulose acetate films;
- in lubricants and transmission oils;
- as an industrial sealant;
- as a plasticiser; and
- as a flame retardant.

The chemical is commonly present in fire retardant mixtures, including Firemaster® 550 that is used in Australia e.g. in building materials.

International

The following international uses have been identified through the Organisation for Economic Co-operation and Development Screening information data set Initial Assessment Report (OECD SIAR, 2002); the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; Galleria Chemica; the European Commission Cosmetic Ingredients and Substances (CosIng) database; the United States (US) Environmental Protection Agency (EPA) Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US National Toxicology Program (NTP); the Substances and Preparations in Nordic countries (SPIN) database; the World Health Organisation (WHO) Environmental Health Criteria 111 (WHO, 1991); the US EPA Flame Retardants Used in Foam An Alternative Assessments Update (US EPA, 2015); the Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile for Phosphate Ester Flame Retardants (ATSDR, 2012); the Environmental Working Group (EWG) Skindeep database; Compilation of Ingredients Used in Cosmetics in the United States (CIUCUS, 2011); and the US Personal Care Products Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary.

The chemical has reported cosmetic uses in:

- nail polishes and enamels; and
- manicuring preparations.

The chemical has reported domestic uses in:

- indoor and outdoor adhesives and sealants;
- coatings, lacquers, and varnishes; and

- paints and inks.

The chemical has reported commercial uses:

- in roofing paper;
- in polyurethane foam;
- in plastics and rubber;
- in electronic products;
- in textiles;
- in hydraulic fluids and lubricants;
- in cellulose acetate film;
- as a flame retardant; and
- as a plasticiser.

The chemical has reported site-limited uses:

- in hydraulic fluids and lubricants.

The chemical is reported to be present in foam-based furniture and baby products (Stapleton et al., 2009; Stapleton et al., 2011) as part of fire retardant mixtures such as Firemaster® 550, and is commonly detected in dust including Australian living rooms and cars (Harrad et al., 2016).

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).

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

The chemical has an exposure standard of 3 mg/m^3 time weighted average (TWA) (Safe Work Australia).

International

The following exposure standards are identified (Galleria Chemica).

An exposure limit of 3 mg/m^3 TWA in different countries such as Austria, Belgium, Canada, Denmark, Finland, France, Greece, Iceland, Indonesia, Ireland, Korea (South), Malaysia, Mexico, Norway, Philippines, Portugal, Russia, Singapore, South Africa, Spain, Switzerland, and the US.

Temporary Emergency Exposure Limits (TEELs) defined by the US Department of Energy (DOE) for the chemical are reported as:

- TEEL-1 = 9 mg/m^3;
- TEEL-2 = 360 mg/m^3; and
- TEEL-3 = 2100 mg/m^3.

Health Hazard Information

Toxicokinetics

Only limited information is available for the chemical.

Experimental data

No information is available for the absorption via the oral route. However, the phosphate triesters are generally readily absorbed via the oral route (Sjogren et al., 2010). The chemical is poorly absorbed through the skin in rats, but is readily absorbed through guinea pig skin (Danish EPA, 2000).

Based on an in vitro Wistar rat liver homogenate assay, the chemical is decomposed via hydrolysis to diphenyl phosphate (DPHP; CAS No 838-85-7), the only major metabolite reported (OECD SIAR, 2002; REACH).

In an in vitro primary human hepatocyte study, TPHP was metabolised mainly into DPHP, while other metabolites (mono- and dihydroxylated metabolites, and a metabolite resulting from hydroxylation and O-dealkylation) were produced at 4- to 10-fold lower rates (REACH).

The chemical was reported to dose-dependently accumulate in placenta tissue in Wistar rat dams orally exposed to Firemaster® 550 (containing the chemical) during gestation days 9–18 (0, 300 or 1000?µg/kg bw/day) (Baldwin et al., 2017). However, the chemical did not undergo either gestational or lactational transfer as it was not detected in foetus or pups following maternal exposure during gestation or lactation (Phillips et al., 2016).

The distributions of the TPHP and its main metabolite DPHP were evaluated in zebrafish. The chemicals TPHP and DPHP were mainly detected in the liver and intestine (Wang et al., 2016).

Human data

The available data from biomonitoring studies suggest that the chemical is absorbed, metabolised and excreted via urine in humans.

In a recent study, fingernail painting as a source of TPHP exposure was evaluated in 26 volunteers. The TPHP metabolite, DPHP was evaluated in urine samples (n = 411) before and after applying nail polish containing 0.97 % of TPHP by weight. The

DPHP levels in urine increased nearly 7-fold after fingernail painting ($p < 0.001$). The contribution to absorption of dermal and inhalation exposure were evaluated and skin was reported as the primary route (Mendelsohn et al., 2016).

The chemical was detected in the plasma of human blood donors. The concentrations in plasma ranged between 130 and 150 ng/g plasma (Jonsson et al., 2001).

The chemical and its metabolites including DPHP are commonly detected in urine (Hoffman et al., 2015; Su et al., 2016; Castorina et al., 2017), including in Australia (van den Eede et al., 2015). It is noted that other aryl phosphate ester flame retardants may also contribute to DPHP formation and excretion (van den Eede et al., 2015).

The reported mean (range) urine levels of the TPHP metabolite DPHP in urine samples from Australia were 24 (<0.3–727) and 63 (10.2–225) ng/mL depending on the sampling campaign (van den Eede et al., 2015). The metabolite was detected in at least 97 % of urine samples.

The chemical TPHP was detected in the urine of an aircraft technician at a level of 80 µg/L (Sjogren et al., 2010).

The chemical is also detected in mothers' milk at low levels. The chemical was detected at median level of 4.9 ng/g lipid (range from non-detectable to 140 ng/g lipid) in 86 % of the mothers' milk samples collected from Japan, the Philippines and Vietnam (Kim et al., 2014). In another study, the chemical was detected in pooled human milk samples from pregnant women in Sweden, at levels of 3.2–11 ng/g lipid (Sjogren et al., 2010).

Metabolites of TPHP (para- and meta-OH-TPHP glucuronides) have been detected in the urine of 4 human volunteers from Ottawa, Canada, demonstrating that TPHP hydroxylation and conjugation occurs in humans (Su et al., 2016).

Acute Toxicity

Oral

The chemical has low acute toxicity based on studies following oral exposure. Based on results from a guideline study in rats, the oral median lethal dose (LD50) is >20 000 mg/kg bw.

In an acute oral toxicity study similar to Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401 (Acute oral toxicity), Wistar rats (5/sex/dose) were treated with a single dose of the chemical (20 000 mg/kg bw, in aqueous suspension) by oral gavage. The animals were observed for 14 days. No mortality was observed. Sporadic visceral haemorrhages were reported at necropsy (OECD SIAR, 2002; REACH).

In a non-guideline study, rats (5/sex/dose; strain not specified) were treated with up to 5000 mg/kg bw of the chemical by oral gavage and observed for 8 days. No mortality or clinical signs of toxicity were reported (OECD SIAR, 2002).

In another non-guideline 14-day study, Sprague-Dawley (SD) rats (number and sex not specified) were treated with a single dose of the chemical up to 15 800 mg/kg bw by oral gavage. The LD50 was 10 800 mg/kg. No further details were reported. (OECD SIAR, 2002).

A number of other studies in rats, mice, guinea pigs, hens, and rabbits have reported LD50 values to be greater than the maximum doses of 3000 to 12 500 mg/kg bw (OECD SIAR, 2002).

Dermal

The chemical has low acute toxicity based on studies following dermal exposure. The reported dermal LD50 for the chemical in rabbits is >10 000 mg/kg bw.

In an acute dermal toxicity study similar to OECD TG 402 (Acute dermal toxicity), albino rabbits (5 with intact skin and 5 with abraded skin, sex unspecified) were treated with a single application of 10 000 mg/kg bw of the chemical. No mortality or adverse effects were observed. No further study details were reported (OECD SIAR, 2002; REACH).

In another acute dermal toxicity study similar to OECD TG 402, New Zealand white (NZW) rabbits (male and female) were administered the undiluted chemical on intact dorsal skin under occlusive conditions for 24 hours. Rabbits were observed for 14 days. The reported LD50 was above the maximum dose of 7900 mg/kg bw. No further study details were reported (OECD SIAR, 2002).

Inhalation

Based on available data, the chemical is considered to have low acute toxicity following inhalation exposure.

In an acute inhalation study similar to OECD TG 403 (Acute inhalation toxicity), male CF-1 mice were exposed (whole body) to the chemical as a vapour in a battery jar at concentrations of 363 mg/m^3 for 6 hours (5 mice) and 757 mg/m^3 for 2 or 4 hours (7 mice/duration). Mice were observed for 24 hours. No lethality or signs of toxicity were reported (REACH).

Corrosion / Irritation

Skin Irritation

The chemical is not considered irritating to the skin based on the OECD guideline skin irritation study.

In an OECD TG 404 skin irritation study, NZW rabbits (3 animals, sex unspecified) were exposed to 500 mg of the moistened chemical on clipped dorsal skin (2 × 3 cm) under occlusive conditions. The rabbits were observed for 14 days. No signs of irritation were reported. The irritation index was 0.0 (OECD SIAR, 2002).

Eye Irritation

The chemical may be slightly irritating to eyes. The effects were not sufficient to warrant hazard classification.

In an OECD TG 405 eye irritation study, the chemical (70 mg; neat) was applied to the mucous membranes of the eyes of NZW rabbits (3 animals). Eyes were rinsed 24 hours after instillation. No signs of irritation were reported (OECD SIAR, 2002, REACH).

In a study that was conducted according to US regulations (16 CFR 1500.42), the chemical (100 mg; neat) was instilled in the eyes of rabbits, and left for 4 hours without rinse (6 animals, Group 1) or rinsed out after 4 seconds (3 animals, Group 2). Conjunctival effects were observed in all animals in Group 1. These effects were reversible within 72 hours after application. No ocular effects were observed in any of the animals in Group 2 (OECD SIAR, 2002).

In another OECD TG 405 study, the chemical (100 mg; neat) was instilled into the conjunctival sac of the left eye in NZW rabbits (3/sex) and the eyelids held closed for 1 second. In 3 animals, the compound was washed out of the eye after 30 seconds. Mild conjunctival effects (slight redness) were reported in all exposed eyes at 24 hours after application. The effects were reversed at 48 hours for all washed eyes and 1 out of 3 unwashed eyes. Only one unwashed eye had slight redness at 27 hours after application and all signs of irritation were reversible by day 6 (OECD SIAR, 2002).

Sensitisation

Skin Sensitisation

The chemical is not expected to be a skin sensitiser. The chemical did not induce dermal sensitisation when tested according to the OECD TG 406 skin sensitisation study. Few human case studies on potential skin sensitisation have been reported (see **Observations in Humans**). However, the incidence of skin sensitisation is very low.

In an OECD TG 406 guinea pig maximisation test (GPMT), 10 male Dunkin-Hartley guinea pigs received intradermal injection of 5 % w/w of TPHP in arachis oil followed by topical induction 7 days later with 75 % w/w of TPHP in arachis oil. Topical challenges (50 % and 75 % w/w of TPHP in arachis oil) were given on day 21. A 0 % (0/10) sensitisation rate was reported. Therefore the chemical is considered not to be a skin sensitiser (OECD SIAR, 2002; US EPA, 2015; REACH).

Observation in humans

No skin sensitisation reactions to the chemical were reported for 343 or 174 patients in human patch tests (exposure concentration and duration not specified). An irritation reaction was reported in one patient (OECD SIAR, 2002; US EPA, 2015).

The low potential for skin sensitisation is supported by human patch test results in 23,192 patients (exposure concentration and duration not specified). Only 15 positive reactions were reported (0.065 %) to cellulose acetate film containing 7–10 % of TPHP. The sensitisation reaction was reported specific to TPHP in only 2 cases (OECD SIAR, 2002; US EPA, 2015).

Single human case studies have reported allergic dermatitis from the chemical when present in plastic articles (such as eyeglasses and hearing aids) or in cellulose acetate film (OECD SIAR, 2002; US EPA, 2015; HSDB).

Repeated Dose Toxicity

Oral

Based on the available information, the chemical is not considered to cause serious damage to health from repeated oral exposure.

In a 90-day study conducted according to OECD TG 408, Wistar rats (10/sex/dose) were fed a diet containing 0, 300, 1500 and 7500 ppm of the chemical. The mean intake over the study period was 0, 20, 105, and 583 mg/kg bw/day for males and 0, 22, 117, and 632 mg/kg bw/day for females. No treatment-related mortality was reported. No toxicologically relevant clinical signs were reported at any doses. Treatment-related increases in liver weights were observed at 7500 ppm in 30 % and 21 % of males and females, respectively. However, no histopathological changes in the liver were reported. Based on the effects on liver weight, a no observed adverse effect level (NOAEL) of 1500 ppm (corresponding to an intake of 105 mg/kg bw/day and 117 mg/kg for males and females, respectively) was reported (REACH).

In a 90-day non-guideline study, rats (sex and strain unspecified) were orally administered (gavage) the chemical at doses of 0, 380 and 1900 mg/kg bw/day. No toxic effects were reported. The NOAEL established was 1900 mg/kg bw/day (OECD SIAR, 2002; US EPA, 2015).

In a 120-day non-guideline study, male SD rats (10/dose) were fed a diet containing 0, 0.25, 0.5, 0.75 or 1 % of the chemical (corresponding to 0, 161, 345, 517 and 711 mg/kg bw/day). A slight depression in body weight gain was observed at estimated doses of 345 mg/kg bw/day and above. A no observed effect level (NOEL) of 161 mg/kg bw/day was reported (Sobotka et al., 1986; OECD SIAR, 2002; US EPA, 2015).

In a 120-day non-guideline immunotoxicity study, Spartan SD rats (10/sex/dose) were fed a diet containing 0, 0.25, 0.5, 0.75, and 1 % of the chemical (98 % pure) (estimated dose of 0, 161, 345, 517 and 711 mg/kg bw/day). No effects were reported on the immune system. A reduction in body weight gain was reported at an estimated dose of 711 mg/kg bw/day. The NOEL was 517 mg/kg bw/day (Hinton et al., 1987; OECD SIAR, 2002; US EPA, 2015).

Dermal

Based on the available information, the chemical is not considered to cause serious damage to health from repeated dermal exposure.

In a 3-week repeated dermal toxicity study similar to OECD TG 410, NZW rabbits (10/sex/dose) received the chemical (50 % solution in ethanol) applied to the intact or abraded skin at doses of 0, 100 or 1000 mg/kg bw/day, 5 days a week. After each

application, the chemical was left on skin for 6 hours under open conditions. No toxicologically relevant adverse effects were reported (OECD SIAR, 2002; US EPA, 2015; REACH).

Inhalation

No experimental data are available for the chemical. However, based on the available observations in employees exposed to the chemical via inhalation, the chemical is not considered to cause serious damage to health from repeated inhalation exposure (see **Observations in Humans)**.

Observation in humans

Fourteen employees were exposed to TPHP vapour, mist, or dust over 8–10 years. The average air concentration of the chemical was 3.5–40 mg/m^3. The particle sizes were <1 µm for majority of the dust (90 %). A slight but statistically significant reduction in red blood cell cholinesterase activity was observed, but no other signs of illnesses were reported (HSDB).

In another study, men (number not specified) were evaluated following exposure to TPHP vapour, mist and dust for 10 years at a concentration of 3.5–40 mg/m^3. No adverse clinical effects were reported (HSDB).

Genotoxicity

Based on available data from in vitro OECD guideline studies, the chemical is not expected to be genotoxic. In vivo genotoxicity data are not available.

The chemical was negative in the following in vitro genotoxicity studies (OECD SIAR, 2002; US EPA, 2015; REACH):

- In an OECD TG 471 bacterial reverse mutation assay (Ames test) with *Salmonella typhimurium* strains TA 1535, TA 100, TA 1537, TA 98 and TA 102 exposed up to 5000 µg/plate of the chemical (in DMSO), with and without metabolic activation with S9 mix.
- In an OECD TG 473 in vitro mammalian chromosome aberration test with Chinese hamster V79 cells exposed to the chemical (in DMSO) for 4 hours, with (10, 20, 40, 50, and 60 µg/mL) and without (3.5, 7, 14, 17.5, and 21 µg/mL) metabolic activation with S9 mix, or in on additional experiment (without metabolic activation) performed using continuous treatment for 18 hours at concentrations of 2.5, 5, 10, 12.5, and 15 µg/mL.
- In an OECD TG 476 in vitro mammalian cell gene mutation test using mouse lymphoma L5178Y cells treated with the chemical at 6.25–75 µg/mL or 3.13–50 g/mL, with and without metabolic activation, respectively.
- In a study similar to OECD TG 482 evaluating unscheduled DNA synthesis in Syrian hamster embryonic (SHE) fibroblast cells treated with the chemical at concentrations of 10 × 10^{-5} to 0.05 M, for 5 hours without metabolic activation in the presence of 3H-thymidine.

Carcinogenicity

Limited data are available for the chemical. The chemical did not induce lung adenomas in mice.

In a non-guideline study (strain-A-mouse lung adenoma assay), male strain A/St mice (20/group) were treated 3 times/week by intraperitoneal injection with the chemical (95–99.9 % purity; neat) at concentrations of 20 (18 total injections, total cumulative dose of 360 mg/kg), 40 (3 total injections, total cumulative dose of 120 mg/kg), or 80 mg/kg bw (single injection). Animals were observed for a further 18 weeks. Treatments did not significantly increase the incidence of lung adenomas when compared to negative controls. The survival rate was 18/20, 3/20, and 12/20 for the 360, 120, and 80 mg/kg bw cumulative dose groups, respectively. The low survival rate observed for the middle dose group may be related to administration route (intraperitoneal), since no mortality was observed for oral, dermal, or inhalation routes in acute toxicity studies at much higher exposure levels (see **Acute Toxicity** and **Repeated Dose Toxicity** sections) (OECD, 2002; US EPA, 2015; REACH).

Reproductive and Developmental Toxicity

Limited data is available for the chemical. Based on the one generation reproductive toxicity study in rats, the chemical is not expected to adversely affect fertility or development. However, a more recent study in zebrafish has suggested potential for developmental effects.

In a one generation reproductive toxicity study similar to OECD TG 415, SD rats (40/sex/group) were fed a diet containing up to 1 % of the chemical (estimated doses up to 690 mg/kg bw/day) for 91 days prior to mating and throughout mating and until end of the study at day 20 of gestation. The chemical did not cause any parental toxicity. Fertility was not adversely affected in either sex, with no significant differences reported between treated and control rats in the implantation efficiency, or the number of pregnancies, corpora lutea, implants, and viable foetuses. The number of early or late foetal deaths and the number of foetal anomalies did not differ significantly between treated and control rats. The NOAEL for male and female fertility, maternal toxicity, and developmental toxicity was 1 % in the diet (690 mg/kg bw/day) (OECD SIAR, 2002; ATSDR, 2012; US EPA, 2015; REACH).

In a 3-week dermal repeated dose toxicity study in NZW rabbits (10/sex/dose) (see **Repeated Dose Toxicity** section) there was no effect on the reproductive organs of rabbits treated with the chemical, up to the highest dose of 1000 mg/kg bw/day (OECD SIAR, 2002; US EPA, 2015; REACH).

In a zebrafish study, wild-type zebrafish embryos (20/treatment, done in triplicate) were exposed to 0.1–10 µM TPHP for 1 hour. Decreased body length and cardiac abnormalities (pericardial oedema and blocked looping of the zebrafish heart) during embryogenesis were reported. The cardiotoxicity was mediated through an aryl hydrocarbon receptor (AHR) independent pathway (US EPA, 2015; McGee et al., 2016).

Other Health Effects

Neurotoxicity

Neurotoxicity is a potential adverse effect of many organophosphates. However, based on available information, the chemical is not considered to cause neurotoxicity.

The chemical did not induce immediate or delayed neuropathy in hens (a standard test model for neurotoxicity) or cats (OECD SIAR, 2002). In addition, while the rat is a poor model for delayed neurotoxic effects, no neurotoxicity was reported in rats exposed to the chemical for 4 months supporting the lack of neurotoxicity observed in other species. Finally, based on human case reports, the chemical has little to no neurotoxic effects after repeated inhalation exposure. Some older studies have reported decreased activity of cholinesterase and paralysis predominantly in cats, but the effects were not reproduced in later studies. This may be due to contamination of the tested samples with other organophosphates (purity not reported; OECD SIAR, 2002).

Experimental data

In a neurotoxicity study in chickens, 5 male leghorn chickens were treated with a single oral (gavage) dose of 1000 mg/kg bw of the chemical. Animals were observed for 14–36 days for signs of neurotoxicity. No signs of paralysis or histological changes in brain, spinal cord, or sciatic nerves were reported. However, the plasma cholinesterase activity at the 24 hr interval after treatment was reduced to 39–65 % of the enzyme activity prior to treatment, depending on the substrate used (acetylcholine, butyrylcholine, methacholine). No significant changes in spinal cord or brain cholinesterases were reported (OECD SIAR, 2002).

In a neurotoxicity study, 2 hens (strain unspecified) received the chemical orally up to 10 000 mg/kg bw (delivered over 2–3 days) in olive oil. The hens were observed for signs of neurotoxicity up to 3 weeks after treatment. No symptoms of neurotoxicity or mortality were reported (OECD SIAR, 2002).

In another study, 4 hens (strain unspecified) were treated with a single oral dose of 500 mg/kg bw of the chemical and observed for 3 weeks. No signs of neurotoxicity were reported. At 24 hours after treatment, cholinesterase activity in the blood was inhibited by 60 % when compared to controls but returned to normal 4 days after treatment in all animals (OECD SIAR, 2002).

In a delayed neurotoxicity study, Rhode Island Red × Light Sussex hens (2/dose) were treated with a single oral (gavage) doses of 2000, 3000, 5000, 8000, or 12 500 mg/kg bw and observed for 2–3 weeks. No signs of toxicity were reported. The NOAEL

was 12 500 mg/kg (OECD SIAR, 2002; US EPA, 2015).

In a study in cats, 5 animals (sex and strain unspecified) were administered single subcutaneous injections of the chemical (99.99 % pure) dissolved in corn oil or propylene glycol, at doses of 400 mg/kg bw (2 cats), 700 mg/kg bw (2 cats), and 1000 mg/kg bw (1 cat). Controls (2 cats) were administered corn oil or propylene glycol. The animals were observed for up to 3 months for signs of neurotoxicity. Within 3–7 days after dosing, some cats became anorexic and prostrate (possibly due to the significant loss of body weight). No evidences of neuropathy (brain and spinal cord) were reported. Blood cholinesterase levels were similar to controls (OECD SIAR, 2002; REACH).

In a 120-day repeat dose toxicity study, male SD rats (10 /dose) were fed a diet containing up to 1 % of the chemical (estimated doses up to 711 mg/kg bw/day) (see **Repeated Dose Toxicity** section). At the end of each month of treatment, neurotoxicity was assessed in open field, accelerating rotarod, forelimb grip strength, and negative geotaxis tests. No effects on neurotoxicity were reported. The NOAEL for neurotoxicity was 711 mg/kg bw/day (Sobotka et al., 1986; OECD SIAR, 2002; US EPA, 2015).

Findings in humans

Slight inhibition of plasma cholinesterase was reported in workers that were engaged in the manufacture of aryl phosphates (including TPHP) and exposed to 0.2 to 3.4 mg/m3 of the chemical in the air. However, cholinesterase inhibition did not correlate with minor gastrointestinal or neuromuscular symptoms reported (NTP).

No neurological issues were reported in workers employed in a TPHP manufacture factory for 2–10 years (NTP).

Endocrine Disruption

Recent studies suggest that the chemical can cause perturbations to the endocrine system, manifesting as hormonal and/or metabolic changes.

In a reproduction study in zebrafish, adult zebrafish were exposed to TPHP (0, 0.04, 0.2, or 1.0 mg/L) for 21 days. Significant decreases in fertility, along with significant increases of plasma 17β-oestradiol (E2) concentrations, vitellogenin levels, and E2/testosterone and E2/11-ketotestosterone ratios were reported (Liu et al., 2013).

In another study, endocrine activity was investigated using a zebrafish model as well as a human adrenocortical cell line (H295R cells) and a breast carcinoma cell line derived from MCF-7 (MVLN cells):

Zebrafish were exposed to TPHP for 14 days, after which sex hormone levels and steroidogenesis related gene expression were determined. Compared to the control, plasma testosterone and E2 concentrations were significantly increased in TPHP treated females, while 11-ketotestosterone concentrations remained unchanged. In males, significantly decreased plasma testosterone and 11-ketotestosterone levels, and increased E2 levels were reported. In both sexes, expression of Cyp17 and Cyp19a genes that are involved in the biosynthesis and metabolism of sex hormones were significantly upregulated. The vitellogenin gene was down- and up-regulated in female and male fish, respectively.

Sex hormone synthesis and steroidogenic gene expression were measured using H295R cells. Treatment of H295R cells with the chemical significantly increased production of testosterone and E2 leading to significantly elevated concentrations in the cell media. Gene expressions of steroidogenic enzymes were up-regulated (Liu et al., 2012).

Estrogen receptor (ER) binding activity of the chemical was evaluated in MVLN cells. The chemical inhibited ER binding by acting as a receptor antagonist (Liu et al., 2012; US EPA, 2015; HSDB).

In an in vitro study, COS-1 cells expressing human glucocorticoid receptor (GR), progesterone receptor (PR), androgen receptor (AR) and estrogen receptor-a (ERa), were treated with up to 10 nM of TPHP. GR and AR activity were inhibited by TPHP by 20 % and 40–50 %, respectively (Honkakoski et al., 2004).

In a study that investigated the thyroid hormone activity of TPHP, exposure to TPHP in rat GH3 pituitary cells (1, 10, or 100 µg/L) and rat FRTL-5 thyroid follicular cells (0, 1, 3, or 10 mg/L) caused upregulation of genes involved in thyroid hormone synthesis. In zebrafish larvae, TPHP exposure caused increased triiodothyronine (T3) and thyroxine (T4) concentrations and increased expression of genes involved in thyroid hormone synthesis (Kim et al., 2015).

In an in vitro study, human primary pre-adipocytes were differentiated in the presence of 0–20 µM TPHP for 14 days. The TPHP induced adipogenesis, as demonstrated by lipid accumulation and expression of adipogenic markers. Global gene expression

analysis showed that TPHP likely exerts its adipogenic effects through the peroxisome proliferator-activated receptor γ (PPAR γ) (Tung et al., 2017).

A recent epidemiological study supports the endocrine active potential of the chemical detected in in vitro and non-mammalian assays. House dust from the homes of 50 men recruited through an infertility clinic were analysed for the chemical. Each interquartile range (IQR) increase in TPHP was associated with a 10 % increase in serum prolactin levels, and a 19 % decrease in sperm concentrations (Meeker and Stapleton, 2010; US EPA, 2015; HSDB).

No evidence of adverse effects was found in a one generation reproductive toxicity study in rats treated up to high doses of TPHP (690 mg/kg bw/day) (see **Reproductive and Developmental Toxicity** section).

Risk Characterisation

Critical Health Effects

The available data demonstrate that TPHP has a low acute and chronic toxicity profiles. The chemical is a potential endocrine active chemical based on in vitro and non-mammalian studies. However, adverse effects were not seen in the most relevant mammalian in vivo study, a one generation reproduction study in rats.

Public Risk Characterisation

Considering that the chemical may be used in cosmetics and may be present in domestic products, the public could be exposed to the chemical. The public may be directly exposed via nail painting products. The public can also come into contact with articles or coated surfaces containing the chemicals, although it is expected that the chemicals will be bound within the articles or coated surfaces. The chemical is also detected in baby products overseas (Stapleton et al., 2011), although the use of the chemical in such products in Australia is unknown. The chemical could be released from articles through, for example, abrasion or dissolution (ATSDR, 2012). The chemical is commonly detected in house dust (Stapleton et al., 2009; Meeker and Stapleton, 2010; Harrad et al., 2016).

The available data indicate that, although public exposure may occur, it is at a low level. The data for the potential health hazard (endocrine effects) is not conclusive, and adverse effects in humans are not expected based on the findings of a reproductive toxicity study. In general, the hazard profile for the chemical is considered low. Therefore, the chemical is not considered to pose an unreasonable risk. However, if further high quality information becomes available on adverse effects related to endocrine activity of the chemical, further assessment may be required.

Occupational Risk Characterisation

During product formulation 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 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.

The data for the potential health hazard (endocrine effects) is not conclusive, and further information is required to conclusively assess potential adverse effects in humans. In general, the hazard profile for the chemical is considered low. Therefore, the health risks to workers from this chemical is considered to be low.

NICNAS Recommendation

Based on the current available data, there are indications of effects associated with hormonal perturbations in animals treated with the chemical. However, the available data do not demonstrate the potential of the chemical to cause adverse effects. NICNAS will continue to monitor the availability of high quality data emerging on the chemical and determine if further assessment may be required.

The chemical is not recommended for classification and labelling under the current adopted Globally Harmonized System (GHS). This does not consider classification of physical hazards and environmental hazards.

Regulatory Control

Advice for consumers

Products containing the chemical should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from exposure to the chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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