Isopropylated triphenyl phosphate esters: Human health tier II assessment

02 March 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phenol, (1-methylethyl)-, phosphate (3:1)	26967-76-0
Phosphoric acid, (1-methylethyl)phenyl diphenyl ester	28108-99-8
Phenol, isopropylated, phosphate (3:1)	68937-41-7

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 are triaryl phosphate esters with isopropyl groups present in one (CAS No. 28108-99-8) or all (CAS No. 68937-41-7 and CAS No. 26967-76-0) of the phenol moieties. All substances are Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB) substances containing various different constituents. Isopropylated triphenyl phosphates (IPTPP) can have isopropyl substituents at ortho (o), meta (m) or para (p) positions on one, two or three of the phenyl rings. Thus, the number of potential isomers is large. In this assessment, the designation IPTPP refers to isopropylated triphenyl phosphates with an unspecified number of isopropyl groups.

The substances with CAS Nos. 68937-41-7 and 26967-76-0 have also been used specifically for chemicals with three p-positioned isopropyl groups (tris(4-isopropylphenyl) phosphate) or three o-positioned isopropyl groups (tris(2-isopropylphenyl) phosphate), respectively (Sjogren, 2010).

Commercial IPTPP formulations may include mono-, di-, and tri substitutions mainly in the o- and p-positions and may contain other compounds such as triphenyl phosphate (CAS No. 115-86-6) (UK Environment Agency, 2009; Sjogren, 2010).

Import, Manufacture and Use

Australian

As reported under previous mandatory and/or voluntary calls for information, the IPTPP with CAS No. 68937-41-7 has site-limited use in the manufacture of other chemicals.

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

Substances may have commercial uses including:

- in lubricants and greases;
- in resins;
- in lubricants; and
- in hydraulic fluids.

International

The following international uses have been identified through the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; Galleria Chemica; the Substances and Preparations in Nordic countries (SPIN) database; the Organisation for Economic Cooperation and Development High Production Volume chemical program (OECD HPV); the United States Environmental Protection Agency's (US EPA) Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US EPA Flame retardants assessment update (US EPA, 2015), the US EPA Preliminary information on manufacturing, processing, distribution, use, and disposal (US EPA, 2017); Commission for Environmental cooperation (CEC), 2015; the US National Toxicology Program (NTP) document (NTP, 2010) and UK Environment Agency report (2009).

The IPTPP substances are reported to be widely used for both its flame retardant and lubricating properties.

The substances may have domestic uses, including in:

- adhesives and sealants; and
- paints and coatings.

Available North American databases do not give evidence for use of these chemicals in consumer products, indicating that chemicals are not likely to be widely available for these types of domestic uses.

The substances may have commercial uses, including in:

- lubricants and greases;
- epoxy and phenolic resins;
- photochemicals; and
- hydraulic fluids and metal-working fluids.

The substances may have site-limited uses, including in manufacture of flame retarded plastics and textiles, including PVC, polyurethane foams and epoxy and phenolic resins, and hydraulic system fluids.

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

Restrictions

Australian

No known restrictions have been identified.

International

In Maine, 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 Worker Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

There are no specific exposure standards for the substances.

International

A MAK value of 1 mg/m^3 for IPTPP (CAS No 68937-41-7) was identified in Germany (Galleria Chemica).

Health Hazard Information

Toxicokinetics

The substances are expected to be readily absorbed via oral and dermal routes of exposure.

Following single oral administration to rabbits, ortho-substituted IPTPP formulation was metabolised within 24 hours and cyclic metabolites were found in bile for up to 24 hours post-exposure (REACH; US EPA, 2015).

Following oral treatment of Wistar rat dams with flame retardant mixture containing IPTPP during gestation days 9–18 (0, 300 or 1000 µg/kg bw/day) (Baldwin et al., 2017), a dose dependent increase in the metabolite isopropyl diphenyl phosphate (CAS No. 28108-99-8) was reported in the urine of pregnant and lactating dams. The chemical did not undergo significant gestational or lactational transfer as it was not detected in foetus or pups following maternal exposure during gestation or lactation (Phillips et al., 2016).

In two in vitro dermal absorption studies with limited reported data, absorption rates for commercial formulations of IPTPP were investigated using human epidermis. Two different components of IPTPP commercial formulations were identified as triphenyl phosphate (TPP; CAS No. 115-86-6) and 2-isopropylphenyl diphenyl phosphate (CAS No. 28108-99-8). Absorption rates for these two components of IPTPP were 0.67–0.9 and 0.54–3.32 µg/cm^2/hr, respectively. A steady state in the blood was achieved within one hour following treatment (US EPA, 2015).

Highly specific metabolic pathways exist for certain aryl phosphate esters and can result with neurotoxic metabolites:

1. The ortho-methyl phenyl (cresyl) isomers can be oxidised to hydroxymethyl species, then to aldehyde and carboxylic acid, followed by conversion to the neurotoxic cyclic phenyl saligenin phosphate (NICNASa). However, alternative degradation pathways leading to inactive excretable products are provided with further substitution of the phenyl ring (i.e. methyl groups in the meta or para positions, in addition to the ortho position) (Sjogren et al., 2010).

2. The para-ethyl phenyl isomers can be hydroxylated to give alpha-hydroxyethyl group, which is then transformed to an acetyl group which leads to potentially neurotoxic metabolites (Eto et al., 1971).

Acute Toxicity

Oral

Based on results from various animal tests following oral exposure to IPTPP, the substances have low acute toxicity. Studies in rabbits and rats orally treated with IPTPP have reported median lethal dose (LD50) of >2000 mg/kg bw (HSDB; REACH; US EPA, 2015).

Dermal

Based on results from acute dermal toxicity studies with IPTPP, the substances have low acute dermal toxicity. The LD50 for IPTPP in rats is >10000 mg/kg bw.

In an acute dermal toxicity study, albino rabbits (five animals with intact skin and five animals with abraded skin) were administered a single dose level of IPTPP (CAS No. 68937-41-7) at 10000 mg/kg bw dermally and observed for 14 days. No mortality was recorded and an LD50 of >10000 mg/kg bw was estimated (REACH; US EPA, 2015).

In another acute dermal toxicity study, Sprague Dawley (SD) rats (3/sex) were administered a single dermal dose of 2000 mg/kg bw of IPTPP (CAS No 26967-76-0) for 24 hours on intact skin under an occlusive wrap. No lethality was reported during the observation time of 14 days (HSDB).

Inhalation

Based on the low acute toxicity in animal tests following inhalation exposure to IPTPP, the substances are not expected to be acutely toxic if inhaled.

In an inhalation study, Wistar rats (5 animals/sex) were exposed to the IPTPP (CAS No. 68937-41-7) as an aerosol at 200 mg/L for one hour by whole body inhalation. No mortality was reported in male rats, while one female died on day seven following treatment. No other effects were reported. A median lethal concentration (LC50) of >200 mg/L was reported (REACH; US EPA, 2015).

Corrosion / Irritation

Skin Irritation

Based on a number of acute dermal irritation tests using a variety of commercial IPTPP formulations, the substances are expected to be, at most, only slightly irritating to the skin (US EPA, 2015). The effects are not sufficient to warrant hazard classification.

No irritation was reported in a dermal exposure study in rabbits with application of 0.5 mL of a formulation containing IPTPP under occluded patches for four hours. No signs of irritation were observed at 4.5, 24, 48 and 72 hours following exposure (US EPA, 2015).

Three New Zealand White (NZW) rabbits were exposed to 0.1 mL of the undiluted IPTPP on shaved backs under semi-occlusive conditions for 4 hours. No irritation was reported and the primary irritation score was 0 (HSDB).

The undiluted commercial IPTPP formulation (0.5 mL) was applied under semiocclusive conditions to intact and abraded skin of 6 albino rabbits for 24 hours and the sites were observed for 72 hours. No irritation was observed (REACH).

Eye Irritation

Based on a number of acute eye irritation tests using a variety of commercial IPTPP formulations, the substances are expected to be slightly irritating to the eyes. The effects are not sufficient to warrant hazard classification.

An undiluted IPTPP formulation (0.1 mL) was instilled in the conjunctival sac of the eyes of 3 rabbits. Slight conjunctival redness in 2 animals with Draize primary irritation scores of 1.3 at 24 hours and zero at 48 and 72 hours was reported (HSDB; US EPA, 2015).

An undiluted commercial IPTPP formulation (0.1 mL) was instilled in the eyes of 9 rabbits. Eyes of 3 rabbits were washed 4 seconds after treatment. At 24, 48, 72 hours and 7 days after treatment, no signs of irritation were observed (HSDB; REACH; US EPA, 2015).

Sensitisation

Skin Sensitisation

Commercial IPTPP formulations were not sensitising to guinea pigs. However, ambiguous sensitisation potential was reported in a local lymph node assay (LLNA) for IPTPP. Based on the weight of evidence of experimental data and the predictions from two quantitative structure activity relationship (QSAR) models, the substances are not expected to be potent skin sensitisers. Therefore, the hazard classification is not warranted.

Commercial IPTPP formulations were not sensitising to guinea pig skin following intracutaneous injection and challenge treatment. One of the IPTPP formulations used contained 70 % of IPTPP (US EPA, 2015).

In a LLNA conducted according to OECD test guideline (TG) 429, four female CBA/J Rj mice were exposed to the IPTPP in acetone/olive oil (4:1 v/v) at 25, 50 or 100 % w/v by topical application on the dorsal surface of each ear, once a day for three consecutive days. Stimulation indices (SI) for 25 %, 50 % and 100 % of the IPTPP were recorded as 7.4, 12.9 and 10.4, respectively. No dose response relationship was observed (REACH; US EPA, 2015).

The IPTPP was not predicted to be a protein binder (QSAR Toolbox) or a skin sensitiser (OASIS-TIMES) in the in silico tests. In addition, other substituted aryl phosphate esters are not skin sensitisers (NICNASa; NICNASb; NICNASc).

Repeated Dose Toxicity

Oral

Based on the adrenal effects seen in repeated oral dose toxicity studies with IPTPP in rats, hazard classification for repeated oral toxicity is warranted for the substances (see **Recommendation** section). Systemic effects in the adrenals are common with other substituted aryl phosphate esters (NICNASa; NICNASb; NICNASc).

In a 91-day repeated dose study according to OECD Test Guideline (TG) 408, Crj:CD(SD) rats (50 animals/sex/dose) were administered 0, 25, 100 or 325 mg/kg bw/day of IPTPP in corn oil by gavage, once daily for 91 days. The body weight gain was significantly reduced in males at the highest dose. Tan discolouration, enlargement and diffuse vacuolation of the adrenals, characterised by enlarged cells with foamy cytoplasm, were reported in males and females at 100 and 25 mg/kg bw/day and above, respectively. The changes were minimal to severe and the severity was dose-dependent. Changes in organ weights were observed in the liver for both sexes at 100 mg/kg bw/day, in the thyroid in males at 325 mg/kg bw/day, and in the ovaries in females at all doses. These changes correlated to centrilobular or panlobular hypertrophy in the liver, follicular cell hypertrophy in the thyroid and interstitial cell vacuolation in the ovaries. Following the recovery period, diffuse vacuolation in the adrenals was not present but cells near the zona reticularis had large single cytoplasmic vacuoles (identified as increased vacuolation). Based on the magnitude of the organ weight increases for adrenals and ovaries, the findings were also considered adverse in females at all dose levels. A lowest observed adverse effect level (LOAEL) of 25 mg/kg bw/day was reported based on changes

in the adrenals in both sexes at all doses. A no observed adverse effect level (NOAEL) was not determined in this study (US EPA, 2015).

In a combined repeated dose and reproductive toxicity study conducted according to OECD TG 422, a commercial IPTPP formulation in corn oil was administered in Crl:CD(SD) IGS BR rats (12 animals/sex/dose) at 0, 25, 100 or 400 mg/kg bw/day, once daily for 14 days prior to mating and 14 days during mating (total of 28 doses for males). Females were further treated during gestation and up to 4 days postpartum for a total of up to 53 days. Increased salivation at 100 and 400 mg/kg bw/day and excessive pawing of the cage was observed in both sexes at 400 mg/kg bw/day. Mean body weights in the parent males and females were unaffected throughout the study. Statistically significant increases in the absolute and relative adrenal (associated with vacuolisation of adrenal cortical cells) and liver weights (corresponding to centrilobular hepatocellular hypertrophy) were observed in males at 100 and 400 mg/kg bw/day and in females at 25 and 100 mg/kg bw/day. Other effects included decrease in mean absolute and relative epididymis weights in males at 400 mg/kg bw/day and increases in thyroid/parathyroid relative weights in males at 100 mg/kg bw/day. Results indicated treatment-related changes in specific organ weights at all dose levels (Great Lakes Chemical Corporation, 2004). A NOAEL was not determined. A LOAEL of 25 mg/kg bw/day was reported based on treatment-related organ weight changes and adrenal effects in females (REACH; US EPA 2015).

In a 28-day study, SD rats (10 animals/sex) were treated with a commercial IPTPP formulation in diet at approximately 0, 91, 460 or 910 mg/kg bw/day. Mortalities were 4/10 (91 mg/kg bw/day) and 4/10 (460 mg/kg bw/day) and 3/10 (910 mg/kg bw/day), but were reported not to be treatment related (US EPA, 2015). Reduction in feed consumption was observed at 460 mg/kg bw/day in both sexes and females in the 910 mg/kg bw/day dose group were observed to have reduced body weight gain. Unspecified abnormalities in clinical chemistry were reported at 460 and 910 mg/kg bw/day. Elevated relative liver weights were observed in all treated groups, but were considered as adaptive. No histopathological lesions were seen in the liver or kidneys at 910 mg/kg bw/day. Based on a limited study details, a NOAEL of 91 mg/kg bw/day was reported based on unspecified abnormalities in clinical chemistry (US EPA, 2015).

Dermal

Based on the effects in the adrenals observed at 500 mg/kg in a 28 day study, hazard classification for repeated dermal toxicity is recommended for the substances (see **Recommendation** section).

In a 28-day study conducted according to OECD TG 410, RAIF rats (5 animals/sex/dose) were treated with the commercial IPTPP formulation under semiocclusive conditions at 40, 200 or 1000 mg/kg bw/day for 5 days per week, 6 hours/day. No adverse effects were reported at 200 mg/kg bw/day. At the highest dose, the males had a decrease in absolute and relative testicular weights. A NOAEL of 200 mg/kg bw/day was based on the effect on testicular weight in males (REACH; US EPA, 2015).

In another OECD TG 410 study, F3 hybrid of RII/1/Tif rats were administered commercial IPTPP formulation at doses of 100, 500 or 2000 mg/kg bw/day by semiocclusive patch on shaved backs for 5 days per week, 6 hours/day for 4 weeks. Females in the 500 mg/kg bw/day dose group and both sexes at 2000 mg/kg bw/day showed slight inhibition of plasma cholinesterase activity. Males in the 2000 mg/kg bw/day dose group showed significant inhibition of erythrocyte cholinesterase activity. Increased adrenal weights were reported in males at 500 and 2000 mg/kg bw/day. Slight fatty changes in the adrenal cortex were observed in 2/5 males at 500 mg/kg bw/day and in 3/5 males at 2000 mg/kg bw/day. NOAELs of 100 mg/kg bw/day for males and 500 mg/kg bw/day for females were determined (REACH; US EPA, 2015).

Inhalation

Based on the available data, hazard classification for repeated inhalation toxicity is warranted for the substances (see **Recommendation** section).

In a non-guideline 90-day study, Fischer 344 (F344) rats (20 animals/sex/dose), male golden Syrian hamsters (20 animals/dose) and NZW rabbits (4 animals/sex/dose) were continuously exposed to the aerosols of commercial IPTPP formulation by whole body inhalation at 10 mg/m^3 or 100 mg/m^3.

Rats in the 100 mg/m^3 dose group showed kyphosis (excessive outward curvature of the spine causing hunching of the back) with rough coats and a general unkempt appearance throughout the course of the study. Body weight gain was reduced at the

highest dose in females, but not in males. Relative liver weights were significantly increased in male and female rats at the highest dose. Testicular atrophy and adrenal enlargement was reported in males at the highest dose and adrenal enlargement in females at both doses. Histopathology showed mild goblet cell hyperplasia of the nasal mucosa in males and in females at the highest dose. Mild hepatocellular swelling was also reported in males females at the highest dose. Hypertrophy of ovarian interstitial cells was seen in 95 % of females at 100 mg/m^3 and 30 % at 10 mg/m^3. Mild to severe degeneration of seminiferous tubules was noted in all males at 100 mg/m^3.

The highest dose was lethal to all 4 rabbits. Clinical signs of toxicity included anorexia, lethargy followed by cachexia accompanied by head droop prior to death in rabbits at 100 mg/m^3. Other effects included chronic nasal inflammation in three males, lymphocytic interstitial inflammation in the lungs in two males, centrilobular to panlobular hepatocellular fatty change in the livers of four females in the 100 mg/m^3 and degenerative neurological lesions in the spinal cord of one female at 10 mg/m^3.

Hamsters in the 100 mg/m^3 dose group were reported to show slightly depressed weight gain. No other effects were seen in hamsters. A lowest observed adverse effect concentration (LOAEC) of 10 mg/m^3 was established in this study based on organ changes in rats. A no observed adverse effect concentration could not be determined in rats (REACH).

Genotoxicity

Based on the available in vitro and in vivo genotoxicity studies on the commercial IPTPP 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) and in vivo (chromosome aberration assays, micronucleus assay and a sister chromatid exchange assay) tests for gene mutation and clastogenicity were negative (HSDB; REACH; US EPA, 2015).

In vitro studies

- Two Ames tests in five strains of *Salmonella typhimurium* at doses up to 100 µL of 1% v/v solution in dimethyl sulfoxide (DMSO) gave negative results, both in the presence and absence of metabolic activation; and
- The DNA damage and repair assay in rat hepatocytes gave negative results at doses of 0.6, 3, 15 or 75 nL/mL.

In vivo studies

- Two chromosome aberration assays in hamsters at 1250, 2500 or 5000 mg/kg bw showed weak mutagenic activity in somatic cells;
- A micronucleus assay in female mice at single oral doses of 100, 500, 1000, 10000 or 50000 mg/kg gave negative results;
- Sister chromatid exchange (SCEs) assay in Chinese hamsters did not show any effect on chromosome exchange; and
- Recessive lethal assay of *Drosophila melanogaster* males was negative for genotoxicity.

Carcinogenicity

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

Reproductive and Developmental Toxicity

Based on the results from reproductive and developmental toxicity studies in rats, hazard classification for reproductive toxicity is recommended. Testicular damage was also observed in several repeat dose studies (see **Repeated dose toxicity** section). Similar effects are observed with other substituted aryl phosphates (NICNASa; NICNASb; NICNASc). In contrast to the neurotoxicity, the data are not sufficient to demonstrate that the reproductive toxicity would be specific to certain isomers.

In a reproductive toxicity study conducted according to OECD TG 421 in SD rats (12 animals/sex/dose), commercial IPTPP formulation containing 90 – 100 % of IPTPP was administered by gastric intubation at 400 mg/kg bw/day. Males were treated for total of 42 consecutive days, starting at 14 days prior to mating and females were treated for up to 54 days. Increased salivation, decrease body weight gain, poor reproductive performance (fertility and fecundity indices were slightly lower), changes in the organ weights in the adrenals (fatty changes) and liver (centrilobular hepatocellular hypertrophy), and vacuolisation of interstitial cells of the ovaries were reported (REACH).

In a combined repeated dose and reproductive toxicity study conducted according to OECD TG 422 (study details provided in the Repeat Dose Study section), decreased fertility in rats was noted at 100 and 400 mg/kg bw/day of commercial IPTPP formulation. Only 50 % of females with evidence of mating were pregnant at 400 mg/kg bw/day. The mid-dose group (100 mg/kg bw/day) also showed signs of reduced fertility (3 females failed to deliver). Only 1 out of 6 litters delivered in the high dose group survived to lactation day 4. The remaining litters in this group were either deceased or euthanised during the study.

Effects on parental reproductive organ weights were reported in both sexes. Effects included increased absolute and relative weights of the epididymis in males, and relative weights of the ovaries in females at doses 25 mg/kg bw/day and above (Great Lakes Chemical Corporation, 2004). A parental systemic and reproductive LOAEL of 25 mg/kg bw/day was reported based on treatment-related changes in the organ weights. A NOAEL could not be determined. For developmental toxicity, a NOAEL of 100 mg/kg bw/day based on decreased litter size and pup survival was reported (REACH; US EPA 2015).

In a 20-day prenatal developmental toxicity study conducted according to OECD TG 414, female Crj:CD(SD) rats (25 animals/dose) were administered commercial IPTPP formulation (approximately 62-68 % IPTPP) at 0, 100, 200 or 400 mg/kg/day in corn oil, orally by a single dose daily from gestational days (GD) 0 to 19. No mortality was reported. Clinical effects observed in rats at 400 mg/kg bw/day after a few days of treatment included decreased activity in one animal, red material around noses and mouths of nine animals, hunched posture in one animal, thin appearance in two animals, brown discoloured facial hair in two animals and brown discoloured hair on the forelimbs in two animals. No treatment-related effects were noted on uterine implantation indices, viable foetuses, post-implantation loss, litter sizes or resorption sites. Mean gravid uterine weights were statistically significantly higher than controls at 200 mg/kg bw/day. Macroscopic examination revealed red or white foci and swollen mucosa of non-glandular portion of the stomach in 3/25 females treated at 400 mg/kg bw/day. No effects were observed on foetal sex ratios, body weights, or visceral and skeletal examinations. A NOAEL for maternal toxicity of 200 mg/kg bw/day and a no observed effect level (NOEL) for developmental toxicity of 400 mg/kg bw/day were reported (REACH).

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 (NICNASb). 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 o-position becomes larger and more branched (see **Toxicokinetics**; Sjogren et al., 2010).

The IPTPP substances in this assessment are not as potent neurotoxins as cresyl phosphate substances. Based on the available data for the commercial IPTPP formulations, the substances have potential to cause neurotoxicity only at very high exposure levels. As with cresyl phosphate substances the toxicity depends on the proportion of o-substitution or other neurotoxic impurities present in the commercial formulations. Unsymmetrical mono-ortho isomers appear to be more toxic in relation to OPIDN than the symmetrical tri-ortho isomers. The data available support classification for isopropylphenyl diphenyl phosphate unless it can be shown that the substance is free of o-isomers (see **Recommendation** section).

Commercial IPTPP formulations

Several commercial IPTPP formulations were tested for acute neurotoxicity in hens. Ataxia was reported only at high doses exceeding 2000 mg/kg bw (Weiner and Jortner, 1999).

In an acute neurotoxicity study, groups of 10 adult domestic hens (*Gallus domesticus*) received a single oral dose of commercial IPTPP formulation at 3000, 5000, 7000 or 9000 mg/kg bw and were observed for 21 days. Eighteen hens each received corn oil

(negative controls) or 500 mg/kg bw tri-o-cresyl phosphate (TOCP) (positive controls). Marked body weight decreases were seen in the positive controls and at the highest dose of IPTPP.

Ataxia was reported in 3/10 hens at 5000 mg/kg bw and 1/10 hens at 7000 and 9000 mg/kg bw each. Hens exhibited effects until the end of the observation period (21 days). Seventeen of 18 positive control hens showed ataxia and serious neuropathological lesions. One bird each at 3000 and 7000 mg/kg bw and two birds at 9000 mg/kg bw had distinct neuropathological lesions, some of which were described as relatively severe. Due to inconsistent dose-response and excessive doses, the findings were inconclusive (Weiner and Jortner, 1999; NTP, 2010).

In another study, hens (6/dose) were administered commercial IPTPP formulation at 5000 mg/kg bw/day by gavage for five consecutive days and observed for 21 days. Mortalities were reported in one bird on day 14. Signs of ataxia were seen on 5/6 treated birds. Evidence of delayed neurotoxicity, particularly axonal degeneration, was observed on histopathological examination of the spinal cords in all treated groups. No NOAEL was calculated (REACH).

In a subchronic gavage study hens were exposed to a commercial IPTPP formulation at doses of 10, 20, 90 and 270 mg/kg bw/day for 13 weeks. Dose dependently increased incidences of ataxia and lesions in the nervous system were observed in the two highest dose levels. The NOAEL was 20 mg/kg bw/day (Weiner and Jortner, 1999)

Isomer specific neurotoxicity

Tri-o-isopropylphenyl phosphate given orally to hens at 1 000 mg/kg bw/day for 4 days did not produce OPIDN, while a single dose of o-isopropylphenyl diphenyl phosphate at 1 200 mg/kg bw caused OPIDN and a 90 % decrease of neuropathy target esterase (NTE) enzyme activity. No OPIDN was induced by 600 mg/kg bw of o-isopropylphenyl diphenyl phosphate (Johnsson, 1975; Sjogren et al., 2010).

Tri-m-isopropylphenyl phosphate, tri-p-isopropylphenyl phosphate, di-p-isopropylphenyl phenyl phosphate and p-isopropylphenyl diphenyl phosphate did not produce OPIDN when given orally to hens at 1000 mg/kg bw as a single dose (Johnsson, 1975; Sjogren et al., 2010).

Tri-o-isopropylphenyl phosphate and p-isopropylphenyl diphenyl phosphate did not produce OPIDN when given to hens at a dose of 1 000 mg/kg bw and 10000 mg/kg bw, respectively, twice daily for six days. However, signs of OPIDN were reported in hens orally administered o-isopropylphenyl diphenyl phosphate at a dose of 1000 mg/kg bw/day, twice daily for 6 days (Johannsen et al., 1977; Sjogren et al., 2010).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects and reproductive toxicity. Neurotoxicity depends on the level of substitution and proportion of o-substitution. In general, effects were only observed at high acute exposures or following repeated exposure.

Public Risk Characterisation

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

The substance IPTPP is used internationally in the manufacture of consumer products (e.g. home furnishings) and as a plasticiser in polymers. Although it is expected that the substances will be bound within the articles or coated surfaces, consumers may be directly exposed to the IPTPP that is released from articles through, for example, abrasion or dissolution (ATSDR, 2012). The IPTPP substances have been detected in the 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. Using a conservative assumption of dust intake of 200 mg/d

(enHealth, 2012) and maximum levels detected in dust reference material, daily intake for toddlers was 13.5 ng/kg bw/day. This gives a margin of exposure of >1800000.

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 IPTPP, leading to adverse health effects is very low. There is particular concern regarding the potential risk of oral exposure to flame retardants in toddlers/children, due to hand-to-mouth behaviour and from sucking on toys or products containing IPTPP. Information is available suggesting that the use of IPTPP substances 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, oral, dermal 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 IPTPP. 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 repeated exposure are implemented. The IPTPP 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 IPTPP 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 IPTPP substances are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

The specific target organ toxicity (single exposure) classification applies only to isopropylphenyl diphenyl phosphate (CAS No. 28108-99-8) unless it can be shown that the substance is free of o-isomers.

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility - Cat. 2 (H361f)
Other Health Effects	Not Applicable	May cause damage to organs - Specific target organ tox, single exp Cat. 2 (H371)

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

- using closed systems or isolating operations;
- 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;
- 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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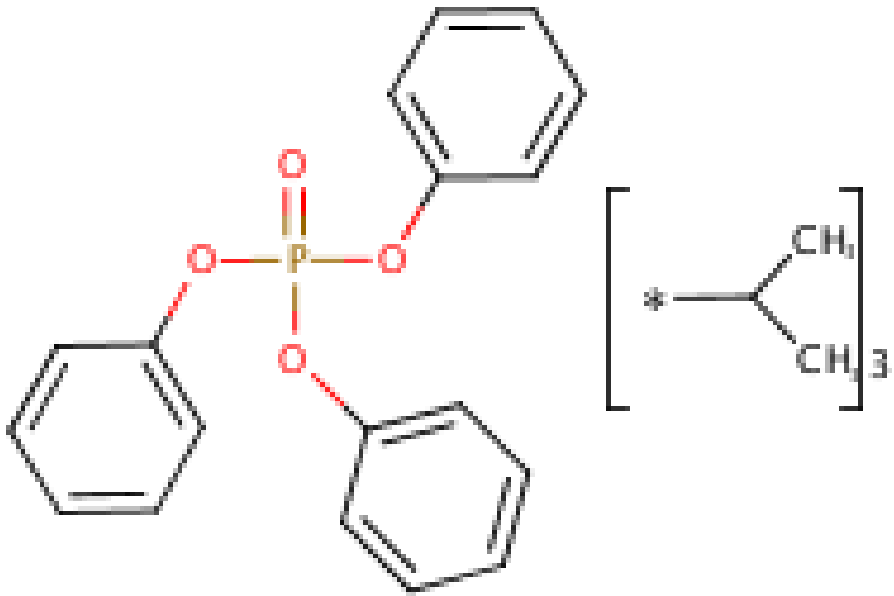
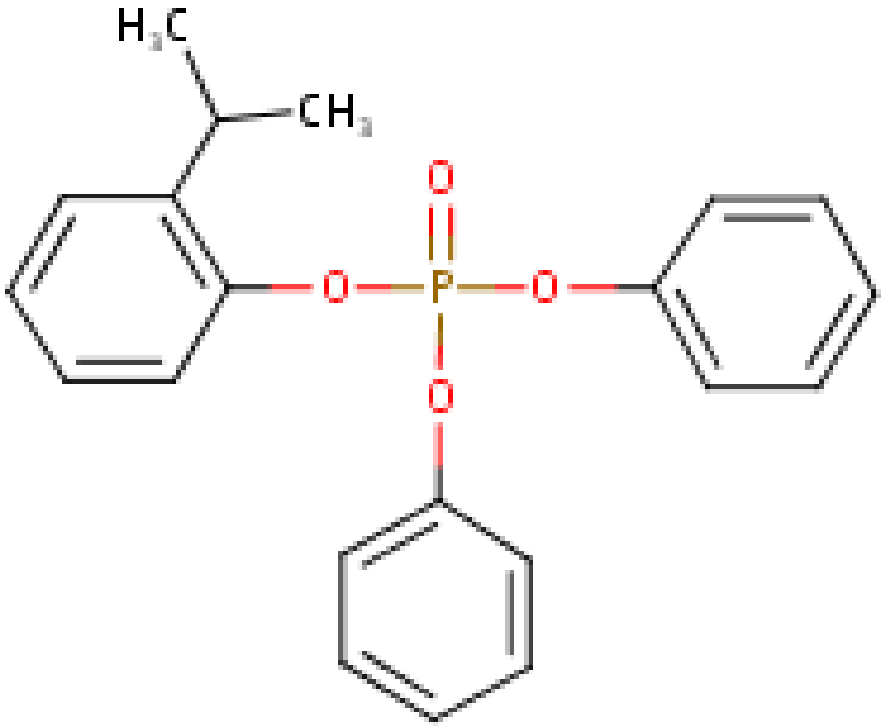
Last Update 02 March 2018

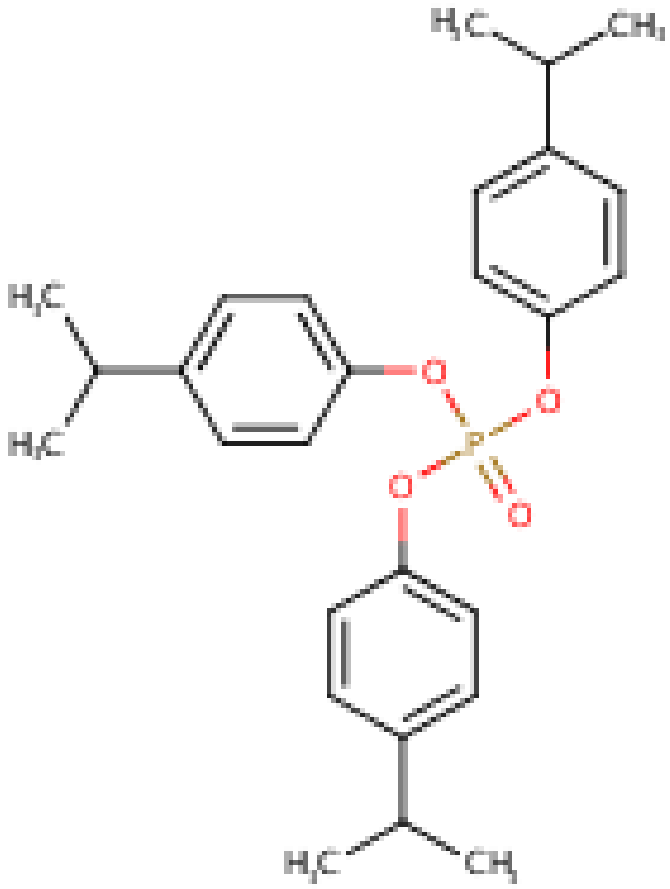
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phenol, (1-methylethyl)-, phosphate (3:1)** tris(isopropylphenyl) phosphate TIPP isopropylated triphenyl phosphate (IPTPP)
CAS Number	26967-76-0
Structural Formula	
Molecular Formula	C27H33O4P
Molecular Weight	452.52

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, (1-methylethyl)phenyl diphenyl ester** isopropylphenyl diphenyl phosphate cumyl diphenyl phosphate monoisopropyltriphenyl phosphate isopropylated triphenyl phosphate (IPTPP)
CAS Number	28108-99-8

Structural Formula	
Molecular Formula	C21H21O4P
Molecular Weight	368.37

Chemical Name in the Inventory and Synonyms	**Phenol, isopropylated, phosphate (3:1)** isopropylated triphenyl phosphate (IPTPP) triaryl phosphates isopropylated phenol isopropylated phosphate Durad 100
CAS Number	68937-41-7
Structural Formula	

	
Molecular Formula	Unspecified
Molecular Weight	369.37

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