Cresyl phosphate isomers – mixed isomers including o-cresol: Human health tier II assessment

02 March 2018

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phosphoric acid, tris(2-methylphenyl) ester	78-30-8
Phosphoric acid, methylphenyl diphenyl ester	26444-49-5
Phosphoric acid, bis(methylphenyl) phenyl ester	26446-73-1
Tar acids, cresylic, phenyl phosphates	68952-35-2

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 group are cresyl phosphate isomers, differing in the methylation degree of the phenol moieties. All substances have the potential to have the phenyl group(s) methylated at ortho position.

The substances cresyl diphenyl phosphate (CAS No. 26444-49-5) and dicresyl phenyl phosphate (CAS No. 26446-73-1) have one or two phenyl rings methylated, respectively, and are mixtures with ortho (o), para (p) or meta (m) methylation. Tri-ortho-cresyl phosphate (TOCP; CAS No. 78-30-8) has all three phenyl rings methylated. Generally, TOCP refers to a chemical with all rings methylated at ortho position (o-o-o), but could also include a mixture isomers with at least one ring methylated at ortho position (o-o-m, o-o-p, o-m-m, o-m-p, o-p-p) (as per the listing in the Hazardous Chemical information system (HCIS) (Safe Work Australia)). Tar acids, cresylic, phenyl phosphates (CAS No. 68952-35-2) refer to the phosphate esters converted from a cresylic distillation fraction derived from tar acid. Tar acid is a complex mixture of phenol and alkyl phenols including cresols and xylenols obtained as a residue from coke ovens and petroleum refining (WHO, 1990). Crude tar acid extracts generally contain phenol, ortho-cresol, meta-cresol, para-cresol and the six isomeric xylenols, and they can be fractionated to give various grades of these products (Rau et al., 1967).

The assessed substances can have similar uses as plasticisers and flame retardants and similar toxicity profiles. They are also present in a commercial Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB) substance, tricresyl phosphate (TCP; CAS No. 1330-78-5). The neurotoxicity of cresyl phosphates has been demonstrated to be isomer specific with ortho isomers (only) inducing organophosphate induced delayed neuropathy (OPIDN; see **Health Hazard Information**).

Import, Manufacture and Use

Australian

No specific Australian use, import, or manufacturing information has been identified for the assessed substances.

However, the use of a related commercial substance TCP (CAS No. 1330-78-5), which is a mixture of various methylated triphenyl phosphate isomers including the chemicals in this assessment, was reported under previous mandatory and/or voluntary calls for information. The total volume of TCP introduced into Australia, was under 10 tonnes.

The following Australian industrial uses were reported for TCP under previous mandatory and/or voluntary calls for information.

The chemical has reported site-limited uses including in manufacturing of:

- polyvinyl chloride;
- rubber;
- nitrocellulose lacquers;
- surface coatings; and
- resins.

International

The following international uses have been identified through Galleria Chemica, the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB) and Occupational Health Database (HazMap), United States Environmental Protection Agency (US EPA) Chemical and Product Categories (CPCat) database; the Substances and Preparations in Nordic countries (SPIN) database; Organisation for Economic Co-operation and Development (OECD), 1998; CEC, 2015; Danish EPA, 2016; and US EPA, 2015.

The substances have possible domestic uses including in:

- coatings and adhesives; and
- surface treatment products (wet proofing).

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

The substances have possible commercial uses including:

- in hydraulic fluids;
- in various rubbers;
- in lubricants;
- in plastics;
- in photographic film, paper, and chemical manufacturing (CAS No. 26446-73-1);
- in polyurethane and insulating foams (CAS Nos 26444-49-5 and 26446-73-1);
- as plasticisers for rubbers and plastics (including food packaging for CAS No. 26444-49-5);
- as flame retardants (including textiles and furniture for CAS No. 26446-73-1); and
- as gasoline additives.

The substances have reported site-limited uses including:

- as additives in extreme pressure lubricants;
- as chemical intermediates; and
- in non-flammable fluids in hydraulic systems.

In addition to the above, the substance TOCP (CAS No. 78-32-0) has reported site-limited uses including:

- as an extraction solvent; and
- as a solvent mixture for various resins.

Similar international uses were also reported for the commercial substance TCP (CAS No. 1330-78-5) potentially containing the chemicals in this assessment (NICNAS). A number of products formulated to contain the assessed chemicals or the TCP as a plasticiser, flame retardant are used in domestic settings and release of the chemical in dust can lead to public exposure (Wu 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).

The commercial substance TCP (CAS No. 1330-78-5), potentially containing the substances in this assessment, is listed on the following (NICNAS):

- EU Cosmetics Regulation 1223/2009 Annex II—List of substances prohibited in cosmetic products;
- New Zealand Cosmetic Products Group Standard—Schedule 4: Components cosmetic products must not contain;
- Health Canada List of prohibited and restricted cosmetic ingredients (the cosmetic ingredient "Hotlist").
- ASEAN Cosmetic Directive Annex II Part 1: List of substances which must not form part of the composition of cosmetic products.

The substance TCP is not approved by the FDA for food contact applications. Cresyl diphenyl phosphate is approved by the FDA as an 'Indirect Additives used in Food Contact Substances' in accordance with the Code of Federal Regulations Title 21 Part 175.

Existing Worker Health and Safety Controls

Hazard Classification

The substance TOCP (CAS No. 78-30-8 listed as tricresyl phosphate (o-o-o-, o-o-m-, o-o-p-, o-m-m-, o-m-p-, o-p-p-)) is classified as hazardous, with the following hazard category and hazard statement for human health in the HCIS (Safe Work

Australia):

Specific target organ toxicity (single exposure) – Category 1; H370 (Causes damage to organs).

Exposure Standards

Australian

The substance TOCP (CAS No. 78-30-8) has an exposure limit of 0.1 mg/m^3 time weighted average (TWA) (Safe Work Australia).

International

The following exposure standards were identified for the substance TOCP (CAS No. 78-30-8; Galleria Chemica):

- exposure limits of 0.02–0.5 mg/m^3 TWA in Russia, China, Abu Dhabi, Austria, Argentina, Belgium, Canada, China, Colombia, Croatia, Denmark, Egypt, Finland, France, Hungary, Iceland, Italy, South Korea, Malaysia, Mexico, New Zealand, Nicaragua, Norway, Peru, Philippines, Poland, Singapore, Portugal, Spain, Switzerland, Taiwan, United Kingdom (UK), United Arab Emirates, Uruguay, United States, Venezuela, and South Africa;
- short-term exposure limits (STEL) of 0.2-0.3 mg/m^3 in Poland, South Africa, Argentina, Egypt, Finland, UK, and Mexico; and
- US Department of Energy, Temporary Emergency Exposure Limits (TEELs); TEEL-1 of 0.3, TEEL-2 of 13 and TEEL-3 of 40 mg/m^3.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value (TLV) for the chemical TOCP (CAS No 78-30-8) of 0.1 mg/m^3 time weighted average (TWA). A skin notation applies. 'This value is intended to minimize the potential for cholinergic effects and the central and peripheral neuropathies that are considered unrelated to its cholinergic activity' (ACGIH, 2011).

Health Hazard Information

The substances in this group are potential constituents of the commercial substance TCP (CAS No. 1330-78-5). The toxicokinetics and the toxicity profile of the assessed substances are expected to be similar to TCP (NICNAS; OECD, 1998; Sherk, 2000; WHO, 2009; MAK, 2016). Therefore, the health hazard information for the TCP is relevant to this assessment.

The toxicity profile of cresyl diphenyl phosphate (CAS No. 26444-49-5), dicresyl phenyl phosphate (CAS No. 26446-73-1), and tar acids, cresylic, phenyl phosphates (CAS No. 68952-35-2) is dependent on the isomeric composition. Only substances identified by these CAS numbers with o-cresyl phosphate content are considered to cause delayed neuropathy (OPIDN; see **Grouping Rationale**).

The Tier II assessment report for the TCP is available at: **https://www.nicnas.gov.au/chemicalinformation/imap-assessments/imap-group-assessment-report?assessment_id=1422**. The report should be read in conjunction with this Tier II assessment.

Toxicokinetics

In a study in F344/N male rats, the distribution and excretion of TOCP at different doses (2, 20 and 200 mg/kg bw/day) was examined. The substance TOCP was excreted primarily in the urine with approximately 70 % appearing in the urine and 20 % in the faeces in 24 hours for all doses. The substance was rapidly distributed to muscle and liver and then adipose tissue and skin. Essentially 100 % of the substance was eliminated after 3 days (NTP, 1994).

The substance TOCP has been demonstrated to be extensively absorbed through cat skin (NICNAS). Whilst dermal absorption studies are not available for the other substances in this assessment, based on data for TOCP and TCP (NICNAS) the substances are expected to be absorbed through the skin.

The substance TOCP is metabolised via three pathways. The first is the hydroxylation of one or more of the methyl groups, and the second is dearylation of the o-cresyl groups. The third is oxidation of the hydroxymethyl to aldehyde and carboxylic acid. The hydroxylation step is critical because the hydroxymethyl TOCP is cyclized to form cyclic phenyl saligenin phosphate (WHO, 1990). Whilst metabolism data are not available for the other substances in this assessment, it is assumed that they can be converted to the cyclic phenyl saligenin phosphate (MAK, 2016).

Acute Toxicity

Oral

The chemicals have moderate acute toxicity based on results from animal tests following oral exposure. Classification based on evident lethality is considered warranted (see **Recommendation** section).

The acute toxicity of TOCP (CAS No. 78-30-8) varies between the species. The chicken and guinea pig are the most sensitive species, while the rat and mice are the least sensitive species. The reported median lethal dose (LD50) values following oral exposure in various species include (WHO, 2009; US EPA, 2015):

- rat 1160, or 8400 mg/kg bw;
- mouse 900 mg/kg bw; and
- chicken 500 mg/kg, or 100-200 mg/kg.

In addition, the lowest reported dose causing lethality in rabbits is 100 mg/kg (ChemID; INCHEM).

The reported LD50 values following oral exposure for cresyl diphenyl phosphate (CAS No. 26444-49-5; the isomer composition of the test substance is not known) include (Galleria Chemica; US EPA, 2015):

- rat 1420, 6400, or 10400 mg/kg bw;
- guinea pig 1600 mg/kg bw; and
- rabbit 1028 mg/kg bw.

No specific information was identified dicresyl phenyl phosphate (CAS No. 26446-73-1) or the phosphate esters of coal tar or petroleum derived cresylic acid (CAS No. 68952-35-2).

Dermal

No data are available for TOCP, dicresyl phenyl phosphate or the phosphate esters of coal tar or petroleum derived cresylic acid.

In a dermal toxicity study using cresyl diphenyl phosphate (CAS No. 26444-49-5) in rabbits (OECD Test Guideline 402), no signs of toxicity were observed at a dose of 2000 mg/kg bw/day (MAK, 2016). An LD50 of >5000 mg/kg bw/day has been reported (OECD, 1998). The isomer composition of the test substances is not known.

Inhalation

No data are available for TOCP, dicresyl phenyl phosphate or the phosphate esters of coal tar or petroleum derived cresylic acid.

In a non-guideline study, no substance related signs of intoxication were observed in male rats exposed for 6 or 7 hours to the saturated vapour of cresyl diphenyl phosphate (OECD, 1998). The isomer composition of the test substance is not known.

Corrosion / Irritation

Skin Irritation

No data are available for TOCP, dicresyl phenyl phosphate or the phosphate esters of coal tar or petroleum derived cresylic acid. Based on data for TCP (NICNAS) and cresyl diphenyl phosphate the substances are not expected to be skin irritants.

In the majority of studies cresyl diphenyl phosphate was reported to be at most slightly irritating to the intact skin of rabbits (MAK, 2016).

Eye Irritation

No data are available for TOCP, dicresyl phenyl phosphate or the phosphate esters of coal tar or petroleum derived cresylic acid. Based on data for TCP (NICNAS) and cresyl diphenyl phosphate the substances are not expected to be eye irritants.

In studies with cresyl diphenyl phosphate was found to be at most slightly irritating to the rabbit eye (MAK, 2016).

Sensitisation

Skin Sensitisation

No data are available for TOCP, dicresyl phenyl phosphate or the phosphate esters of coal tar or petroleum derived cresylic acid. Based on data for TCP (NICNAS) and cresyl diphenyl phosphate the substances are not expected to be skin sensitisers.

In a study with limited documentation, no evidence of sensitisation was observed following challenge treatment with cresyl diphenyl phosphate (MAK, 2016).

Repeated Dose Toxicity

Oral

Limited data are available. Data for cresyl diphenyl phosphate and TCP suggest that the substances may cause damage to health by prolonged exposure. Classification is considered warranted (see **Recommendation** section). Systemic effects in the adrenals observed in animals exposed to cresyl diphenyl phosphate are similar to those seen for TCP, a mixture containing assessed substances.

The substance TCP caused cytoplasmic vacuolization of the adrenal cortex, and ovarian interstitial cell hypertrophy in several studies in rats and mice. A LOAEL of 50 mg/kg bw/day, the lowest dose tested, was identified for both rats and mice in a 13 weeks study (NTP, 1994; US EPA, 2015; Government of Canada, 2016; NICNAS).

Whilst the mechanisms by which the adrenal and ovary effects occur is not fully understood, inhibition of the neutral cholesterol ester hydrolase (nCEH) has been suggested. The enzyme nCEH catalyses the conversion of stored cholesteryl esters in the adrenocortical and ovarian interstitial cells (ATSDR, 2012).

In a 28-day oral gavage study in CD rats with cresyl diphenyl phosphate (44.4 %, free of o-isomers), a no observed adverse effect level NOAEL of 62.5 mg/kg bw/day was reported. The target organs for systemic toxicity were the liver, kidneys and adrenals. No signs indicating neurotoxic effects were observed. Increased liver weights and histopathological changes in the kidney and liver were observed at dose 250 mg/kg bw/day. Fatty vacuolation of the adrenal was observed in animals dosed with 1000 mg/kg bw/day (MAK, 2016).

In a combined repeated dose and reproduction/developmental toxicity study (OECD TG 422) with cresyl diphenyl phosphate (41.9 %, free of o-isomers) (see **Reproductive and developmental toxicity** section) enlargement and cortical vacuolation of the adrenals in both sexes was observed in animals exposed to 60 mg/kg bw/day. In addition, increase of total cholesterol, decrease of cholinesterase activity, and enlargement of the liver were found in male rats, and histopathological changes in the liver, kidneys and the thymus were found in female rats. No effects were observed at doses 12 mg/kg bw/day (OECD, 2002; MAK, 2016). Due to toxicokinetic reasons, the test substances which are free of o-isomers cannot be considered fully representative of all of the substances in this group.

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

The lethal dose for humans by ingestion is estimated about 1000 mg/kg bw of TOCP (CAS No. 78-30-8), while clinical signs including severe paralysis were reported following accidental ingestion of 6–7 mg/kg bw of TOCP (US Occupational health Guideline for Triorthocresyl phosphate, 1978).

Genotoxicity

Limited data is available for the substances.

Cresyl diphenyl phosphate was negative in two bacterial Ames tests and two in vivo mouse micronucleus tests. Whilst an increase in chromosomal damage was observed in vitro in the presence of activation, the evaluation of this study was considered limited due to the number of cells examined (MAK, 2016).

The presence of DNA adducts have been reported in several organs of rats exposed orally to TOCP (Sjogren et al., 2010). However, the substance TCP was negative in several in vitro studies (NICNAS).

Carcinogenicity

No data are available for the chemicals. Based on data for TCP (NICNAS) the chemicals are not expected to be carcinogenic.

Reproductive and Developmental Toxicity

The substance TCP, containing the assessed substances, is recommended for classification as hazardous with hazard category 'Reproductive toxicity – Category 1B' and hazard statement 'may damage fertility (H360F)' (NICNAS). The substance TCP induced functional and structural effects in the male reproductive system and associated reproductive impairment in females (NICNAS). Reproductive effects consistent with those observed with TCP were observed in studies with TOCP and cresyl

diphenyl phosphate. Based on the data available this classification should apply to all the substances in this assessment (see **Recommendation** section).

In contrast to the neurotoxicity of TCP, which is considered due to the metabolite arising specifically from the ortho-substituted isomer, the data is not sufficient to demonstrate that the reproductive toxicity would be specific to certain isomers.

In a 63-day study, Fischer 344 (F344) rats were given 0, 10, 25, 50, 75, or 100 mg/kg bw TOCP daily. Dose-dependent (10 to 100 mg/kg/day) decreases in cauda epididymal sperm motility and density, testicular enzyme activities, and alterations in sperm morphology were observed. The NOAEL was 10 mg/kg bw/day (HSDB).

In a study in Sprague Dawley (SD) rats with TOCP, sperm motility and numbers were reduced in exposed animals following dosing at 150 mg/kg bw/day for 10 days. Irreversible damage to the process of spermatogenesis was observed in animals exposed for 21 days (NICNAS).

Cresyl diphenyl phosphate (41.9 %, free of o-isomers) was tested in a combined repeated dose and reproduction/developmental toxicity study (OECD TG 422). Groups of 10 male and 10 female SD rats received 0, 12, 60 or 300 mg/kg bw/day by gavage. Males were dosed for 41 days and females dosed 14 days prior to mating until day 3 of lactation. At 300 mg/kg bw/day reduced sperm count and degeneration of the germinal epithelium in the testes was observed in 9/10 males. Reduced fertility, implantation rates and birth rates (attributed to the effects in the males) were reported. Effects in the adrenals, kidneys, liver and ovaries were also reported (OECD, 1998; MAK, 2016).

Female CD rats were administered cresyl diphenyl phosphate (44.4 %, free of o-isomers) from days 6 to 15 of gestation in a study conducted according to OECD TG 414. No developmental effects were observed (MAK, 2016).

Other Health Effects

Neurotoxicity

The substance TOCP (CAS No. 78-30-8) is classified as hazardous with hazard category Specific target organ toxicity (single exposure) – Category 1 (H370) and hazard statement 'Causes damage to organs'. This is supported by the numerous reports of TOCP poisoning producing delayed effects on the central and peripheral nervous systems (WHO, 1990).

There are no reports of human effects following exposure to the other substances in this group. However, unsymmetrical mono-ortho isomers of tricresyl phosphate (MOCP) are more toxic (in relation to OPIDN) than those with the di-ortho configuration (DOCP), which in turn are more toxic than the symmetrical tri-ortho isomer TOCP (Craig and Barth, 1999). The phosphate esters of coal tar derived cresylic acids contain the more toxic ortho isomer (Whelan, 1994). Therefore, this classification should apply to CAS Nos. 26444-49-5, 26446-73-1 and 68952-35-2 unless it can be shown they are free of o-isomers.

Experimental – neurotoxicity

Multiple experimental studies were identified on the neurotoxic potential of TOCP (CAS No 78-30-8) and cresyl diphenyl phosphate (CAS No 26444-49-5) or TCP containing ortho isomers to induce delayed neuropathy (INCHEM; NICNAS; MAK, 2016).

In a sub-chronic non-guideline toxicity study, male cats (n=3, except n=10 for 10 mg/kg bw) were treated with a daily dermal dose of 0.5, 1, 5, 10 or 100 mg/kg bw/day of TOCP for 90 days, and surviving cats were kept for a 30-day observation period. All cats treated daily with dermal doses of 5 mg/kg bw/day or above developed signs of delayed neurotoxicity including ataxia and weakness of lower limbs after a delay period that was inversely proportional to the dose (Abou-Donia et al, 1986).

An experiment to investigated effects on axon outgrowth and neurofilament levels in mouse neuro-2a (N2a) neuroblastoma cells by the commercial product (TCP) and purified isomers (TOCP and tri-para-cresyl phosphate). TOCP inhibited the outgrowth of axon-like processes following exposure times of 24 h or longer (Fowler et al., 2001). In another in vitro study with isolated cortical neurons TOCP significantly reduced the size and complexity of neurite networks (Hausherr et al., 2016).

Mono ortho-cresyl phosphate (MOCP) and TOCP inhibited NTE activity in vitro and in vivo in hens. The potency of MOCP was twice that of TOCP (Sprague and Castles; 1985) showing that the delayed neurotoxicity potential is greater in isomers having only one ortho substituent.

Data for diphenyl cresyl phosphate demonstrated isomer specific toxicity.

In a non-guideline study, White Leghorn hens received a single oral dose of 30, 50, or 70 mg/kg bw of cresyl diphenyl phosphate (with o-cresyl phosphate content). Ataxia and inhibition of NTE activity by 90 % in the brain and by 83 % in the spinal cord were reported (MAK, 2016). There was limited evidence of neurotoxicity in a number of studies in rats and hens with cresyl diphenyl phosphate low in ortho-isomers (MAK, 2016).

Humans – neurotoxicity

The substance TOCP produces peripheral neuropathy, OPDIN, in humans. The peripheral neuropathy caused by TOCP exposure is characterised by a one to three week delay in the onset of symptoms. TOCP has been defined as one of the more potent OPIDN neurotoxins in humans. The initial symptoms include muscle cramps and soreness as well as muscle weakness. The symptoms may progress to partial paralysis of the extremities (mild cases) or to complete paralysis (severe cases) (NAS, 2000; Sherk, 2000; WHO, 2009; Sjogren et al., 2010).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are neurotoxicity and reproductive effects. The substances can also cause other harmful effects following acute and repeated exposure.

The neurotoxicity of cresyl diphenyl phosphate (CAS No. 26444-49-5), dicresyl phenyl phosphate (CAS No. 26446-73-1), and the phosphate esters of coal tar or petroleum derived cresylic acid (CAS No. 68952-35-2) is expected to depend on the proportion of ortho-isomers.

Public Risk Characterisation

Given the uses identified for these substances, there is a low likelihood that the public will be exposed significantly. The public could come into contact with articles and coated surfaces containing the substances, although it is expected that they will be bound within the article or coated surface. Some of the substances could be released from articles through e.g. abrasion or dissolution. The TCP substance (mixture of four isomers, isomers not identified) has been detected in house dust (Ali et al., 2012; Wu et al., 2016). However, the concentrations of TCP are low, probably due to its infrequent use as a flame retardant and low release from consumer products because of its low vapour pressure (Ali et al., 2012). Additionally, since the ortho-isomers are being restricted in current commercial products, the risks associated with exposure to the assessed substances is not considered to be unreasonable.

Occupational Risk Characterisation

During handling of the substances, dermal, oral and inhalation exposure of workers to these substances may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical acute and systemic long-term health effects, these substances could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. These 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 these 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 chemicals are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

The specific target organ toxicity (single exposure) classification need not apply to CAS Nos. 26444-49-5, 26446-73-1 and 68952-35-2 if it can be shown that they are free of o-isomers.

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

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Repeat Dose Toxicity	Not Applicable	May cause damage to organs through prolonged or repeated exposure - Cat. 2 (H373)
Reproductive and Developmental Toxicity	Not Applicable	May damage fertility - Cat. 1B (H360F)
Other Health Effects	Not Applicable	Causes damage to organs - Specific target organ tox, single exp Cat. 1 (H370)

[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, dermal, and 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;
- 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 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 have not been undertaken as part of this assessment.

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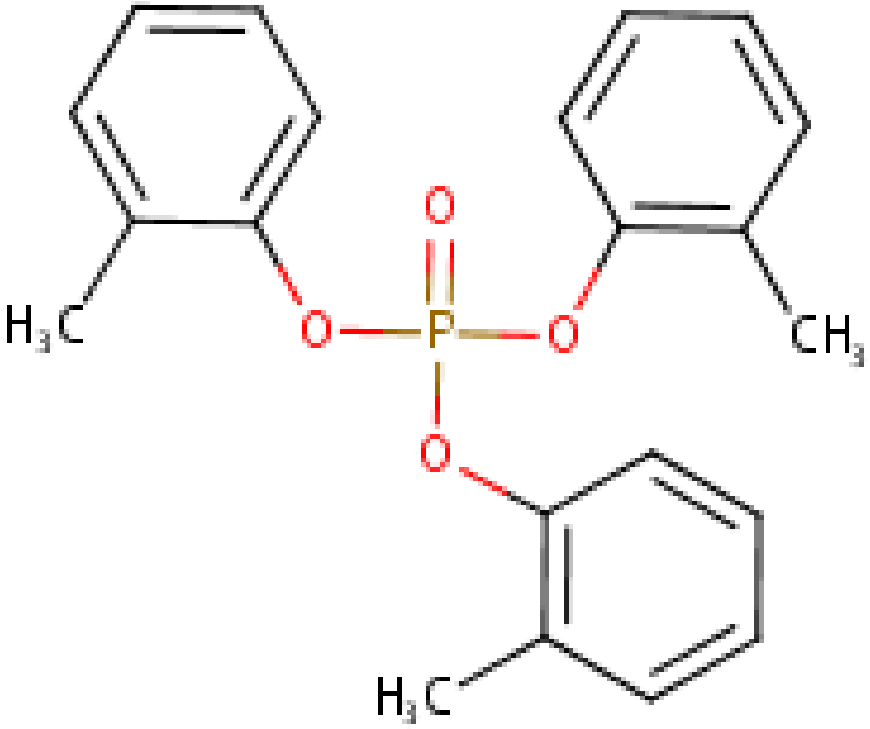
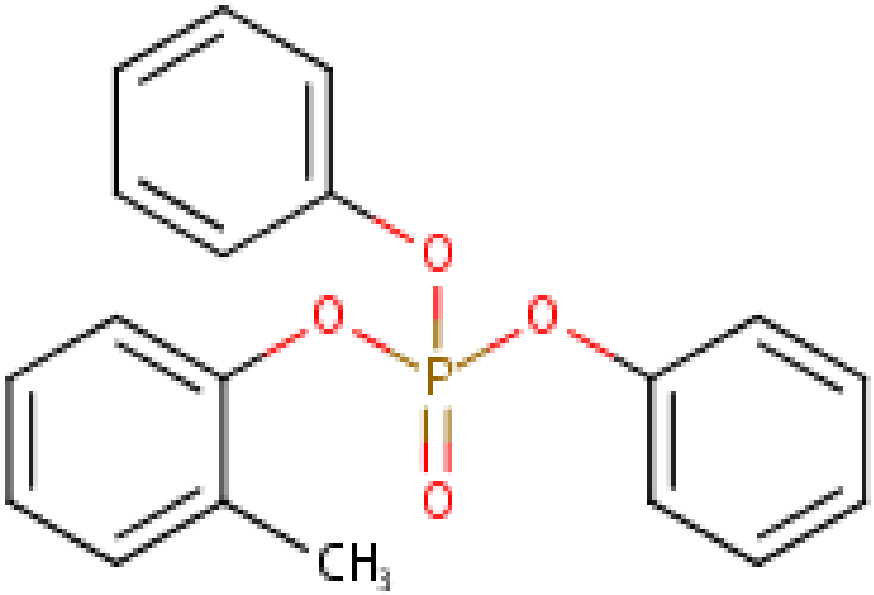
Last Update 02 March 2018

Chemical Identities

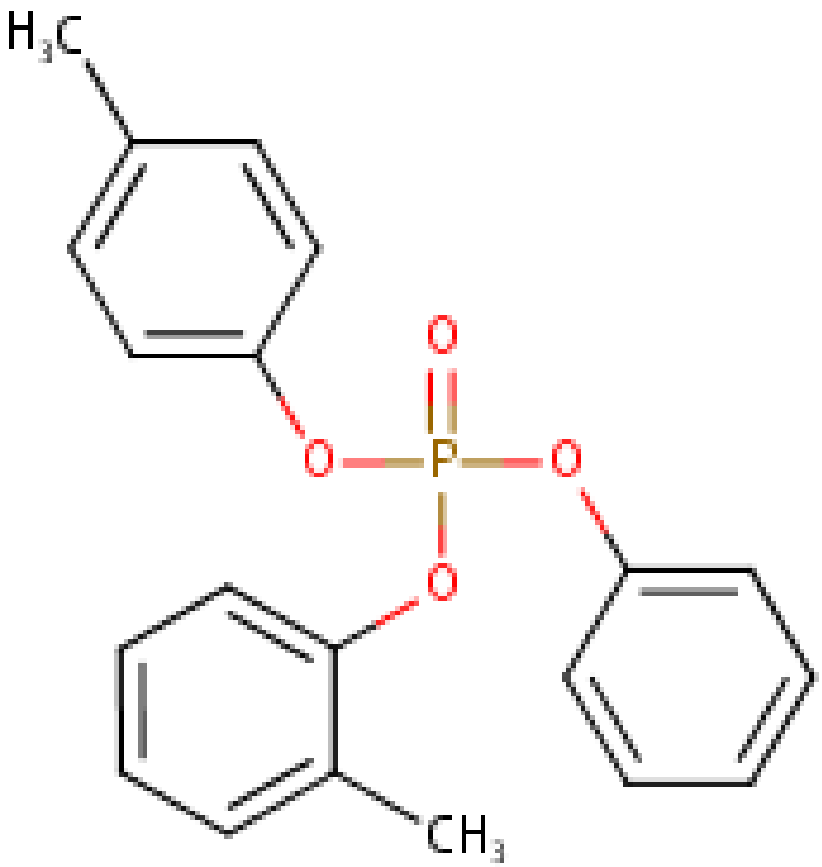
Chemical Name in the Inventory and Synonyms	**Phosphoric acid, tris(2-methylphenyl) ester** tri-ortho-cresyl phosphate TOCP
CAS Number	78-30-8
Structural Formula	

	
Molecular Formula	C21H21O4P
Molecular Weight	

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, methylphenyl diphenyl ester** cresyl diphenyl phosphate
CAS Number	26444-49-5
Structural Formula	

	
Molecular Formula	C19H17O4P
Molecular Weight	

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, bis(methylphenyl) phenyl ester** bis(methylphenyl) phenyl phosphate.
CAS Number	26446-73-1
Structural Formula	

	
Molecular Formula	C20H19O4P
Molecular Weight	

Chemical Name in the Inventory and Synonyms	**Tar acids, cresylic, phenyl phosphates** Phosphate esters of coal tar or petroleum derived cresylic acid
CAS Number	68952-35-2
Structural Formula	**No Structural Diagram Available**

Molecular Formula	Unspecified
Molecular Weight	Unspecified

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