Cresyl phosphate isomers – tri-meta and tri-para isomers: Human health tier II assessment

30 June 2017

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phosphoric acid, tris(4-methylphenyl) ester	78-32-0
Phosphoric acid, tris(3-methylphenyl) ester	563-04-2

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 chemicals in this group are tricresyl phosphate isomers, differing in the position of the methylated carbon atom of the cresol moieties. Tri-meta-cresyl phosphate (TMCP; CAS No 563-04-2) has all three phenyl rings methylated at meta position (m-m-m), while in tri-para-cresyl phosphate (TPCP; CAS No 78-32-0) the three phenyl rings are methylated at para position (p-p-p). Additionally, the chemicals may contain amounts of para- and meta-substituted phenyl rings (m-m-p, m-p-p).

The assessed chemicals 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 chemicals.

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; and US EPA, 2015.

The chemicals have possible domestic uses including in:

- cleaning and washing agents;
- surface treatment products (*wet proofing*); and
- paints, lacquers and varnishes.

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 type of domestic uses.

The chemicals have reported commercial uses including:

- in hydraulic fluids;
- in lubricants;
- in plastics;
- in polyurethane foams;
- in photographic film, paper, plate, and chemical manufacturing (CAS No 78-32-0);
- in construction materials;
- as plasticisers for rubbers and plastics;
- as flame retardants; and
- as gasoline additives.

The chemicals have reported site-limited uses including:

- as additives in extreme pressure lubricants;
- as extraction solvents; and
- in non-flammable fluids in hydraulic systems.

The chemicals may have non-industrial use in non-agricultural pesticides.

Similar international uses were also reported for commercial substance TCP (CAS No 1330-78-5) potentially containing the chemicals in this assessment (NICNASa). 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

No restrictions specific to the individual isomers have been identified.

The commerical substance TCP (1330-78-5), that contains the assessed chemicals, 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.

Existing Worker Health and Safety Controls

Hazard Classification

The chemical TPCP (CAS No. 78-32-0) is classified as hazardous, with the following hazard categories and hazard statements for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia):

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

Acute toxicity – Category 4; H312 (Harmful in contact with skin).

Whilst TMCP (CAS No. 563-04-2) is not specifically listed on HCIS, the entry under CAS No. 78-32-0 is stated to cover all tri-cresyl phosphate isomers containing meta or para methylation (m-m-m-, m-m-p-, m-p-p-, p-p-p-), and therefore, also covering both chemicals in this assessment.

Exposure Standards

Australian

No specific exposure standards are available.

International

The American Conference of Governmental Industrial Hygienists (ACGIH; United States) has issued a notice of intended change for the chemicals with a Threshold Limit Value (TLV) of 0.05 mg/m^3 time weighted average (TWA) (Galleria Chemica).

Health Hazard Information

The chemicals in this group are constitutents of the commercial substance TCP (CAS No 1330-78-5). The substance TCP can contain methylated triphenyl phosphate isomers with an unspecified amount of methyl substitution, but mainly consists of the chemicals in this assessment (US EPA, 2015). Historically, the TCP also contained 25-30 % of ortho residues, but more recently the commercially produced TCP is expected to contain only up to 0.4 % of ortho residues, depending on manufacturing, purification and processing of the substance (US EPA, 2015). Therefore, for most toxicological endpoints, the health hazard information for TCP (CAS No 1330-78-5) is considered relevant to this assessment where the isomer content is specified, as TCP may also contain ortho-substituted isomers. Only the ortho-substituted isomers, and not the meta- or para substituted isomers (assessed chemicals), are considered to cause delayed neuropathy termed organophosphate-induced delayed neurotoxicity (OPIDN) (Craig & Barth, 1999; ATSDR, 2012).

Data are also avaliable for the related chemical, diphenyl cresyl phosphate (CAS No. 26444-49-5). Given both the structural similarities and that this chemical has been tested with no ortho content, the health hazard information is considered relevant to this assessment.

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 Tier II assessment report for cresyl diphenyl phosphate is available at: **https://www.nicnas.gov.au/chemical-information/imap-assessments/imap-group-assessment-report?assessment_id=3470**. These reports should be read in conjunction with this Tier II assessment.

Toxicokinetics

In a study in F344/N male rats, the distribution and excretion of the chemicals at different doses (2, 20 and 200 mg/kg bw/day) were examined. The chemicals were well absorbed after oral administation, although different patterns of excretion were observed. The chemical TMCP was excreted primarily in the faeces at all doses where as TPCP was primarily excreted in the urine at low doses and faeces at high doses. The chemicals were rapidly distributed to muscle and liver and then adipose tissue and skin. Essentially 100 % of both chemicals were eliminated after 3 days (NTP, 1994).

Whilst dermal absorption studies are not available, based on data for TCP the chemicals are expected to be absorbed through the skin (NTP, 1994).

In a study in Wistar rats, TPCP is initially metabolised to p-hydroxy benzyl alcohol. The final metabolite is p-hydroxy benzoic acid which is excreted in the urine. Unlike TOCP, the meta and para cresolphosphate isomers are not metabolised to the cyclic phenyl saligenin phosphate (NTP, 1994; MAK, 2016).

Acute Toxicity

Oral

The chemicals are classified as hazardous with hazard category 'Acute toxicity – category 4 (oral)' and hazard statement ‘Harmful if swallowed’ (H302) in HCIS (Safe Work Australia). The available data for the chemcials and the commercial substance TCP, support the removal of this classification.

The reported medial lethal dose (LD50) values are generally greater than 2000 mg/kg bw for both chemicals. Various LD50 values were reported following oral exposure in various species (WHO, 1990; US EPA 2015; Galleria Chemica).

TMCP (CAS No 563-04-2):

- chicken >2000mg/kg; and

- rabbit 3000 mg/kg bw.

TPCP (CAS No 78-32-0):

- chicken >1000mg/kg;
- rabbit >3000 mg/kg bw; and
- rat >128000 mg/kg bw

Based on LD50 values of >2000 mg/kg bw/day from various studies, TCP is considered to have low acute toxicity in animal tests following oral exposure (NICNASa).

Dermal

The chemicals are classified as hazardous with hazard category 'Acute toxicity – category 4 (dermal)' and hazard statement 'Harmful in contact with skin' (H312) in HCIS (Safe Work Australia). Whilst no data are available for the chemicals, the available data for the commercial substance TCP, support the removal of this classification.

The substance TCP is considered to have low acute toxicity in animal tests following dermal exposure. The LD50 values (rabbit) of > 2000 mg/kg bw/day was reported in various studies (NICNASa).

Inhalation

Based on data for the sustance TCP containing the chemicals in this group (NICNASa), the chemicals are expected to have low acute toxicity following inhalation exposure.

Corrosion / Irritation

Skin Irritation

Based on data for the substance TCP containing the chemicals in this group (NICNASa), the chemicals are not expected to be skin irritants.

Eye Irritation

Based on data for the substance TCP containing the chemicals in this group (NICNASa), the chemicals are not expected to be skin irritants.

Sensitisation

Skin Sensitisation

Based on data for the substance TCP containing the chemicals in this group (NICNASa), the chemicals are not expected to be skin sensitisers.

Repeated Dose Toxicity

Oral

Limited data are available. Data for TCP and the related chemical cresyl diphenyl phosphate (CAS No 26446-73-1), suggest that the chemicals may cause damage to health by prolonged exposure. Classification is considered warranted (see **Recommendation** section).

In a non-guideline study, Sprague Dawley (SD) rats were exposed for 3 months to TCP (60–65% TMCP and 35–40% TPCP) suspended in water with 5% gum arabic at doses of 30, 100, 300, or 1000 mg/kg bw/day (WHO, 1990). Histopathological examination found no treatment-related effects on examined organs including brain, liver, kidneys, spleen, heart, lungs, adrenals, testes and ovaries (REACH, NICNASa).

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 week study (NTP, 1994; US EPA, 2015; Government of Canada, 2016; NICNASa).

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

In repeated dose studies with the related chemical cresyl diphenyl phosphate (stated to be free of o-isomers), histopathological changes in the liver, kidney and adrenal glands (fatty vacuolation) were observed at 60 mg/kg bw/day. No effects were observed at 12 mg/kg bw/day (NICNASb).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on data for the substance TCP containing the chemicals in this group (NICNASa), the chemicals are not expected to be genotoxic.

Carcinogenicity

Based on data for the substance TCP containing the chemicals in this group (NICNASa), the chemicals are not expected to be carcinogenic.

Reproductive and Developmental Toxicity

There is limited isomer specific information available for the chemicals in this group. The available data for the substance TCP (NICNAS) as well as for the related chemical diphenyl cresyl phosphate (CAS No 26444-49-5) suggest that the chemicals are suspected of damaging fertility (see ***Recommendation*** section).

The substance TCP, containing the chemicals in this group, is recommended for classification as hazardous with hazard category 'Reproductive toxicity – Category 1B' and hazard statement ‘may damage fertility (H360F)' (NICNASa). The TCP

induced functional and structural effects in the male reproductive system and associated reproductive impairment in females (NICNASa). 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. Reproductive effects similar with those observed with TCP were observed in studies with the structurally related chemical cresyl diphenyl phosphate that is stated to be free of o-cresyl content.

In a study mainly investigating the testicular toxicity of TOCP, the chemical TPCP was reported non-toxic to the testes of rats (HSDB).

However diphenyl cresyl phosphate (CAS No 26444-49-5; 41.9% purity, free of TOCP and other ortho-isomers), was shown to be reproductive toxicant (MAK, 2016) in a combined repeated dose and reproductive/developmental toxicity study in SD rats (OECD TG 422). Reduced fertility attributed to inhibition of spermiogenisis in male parents was observed (NICNASb).

It was suggested that the testicular toxicity of TCP could be related to the neurotoxic potential and effect on testicular neurotoxic-esterase (NTE) or nonspecific esterase (NSE), of the ortho-substituted isomer (TOCP, CAS No 78-30-8) (Chen et al., 2012). However, the mechanism related to neurotoxic potential is not supported by a structurally related chemical, trixylenyl phosphate (CAS No 25155-23-1). In a combined oral repeated dose and reproductive/ developmental toxicity study using SD rats (OECD TG 422), trixylenyl phosphate was shown to have no effects on functional performance and motor activity but caused dose-dependent changes in testis, epididiymis and ovarian weights as well as in histopathology (ECHA, 2010). This is supported by the finding that further substitution in the phenyl ring containing the ortho-substituent greatly reduces the neurotoxicity by providing alternative degradation pathways (Sjogren et al., 2010). This shows that reduced neurotoxicity is not accompanied by reduced testicular toxicity.

Other Health Effects

Neurotoxicity

Some triaryl phosphates cause organophosphorus pesticide neurotoxicity (OPIDN), a neurodegenerative disorder characterised by a delayed onset of prolonged ataxia and upper motor neuron spasticity. For compounds with a pentavalent phosphorus atom, the presence of the ortho methyl group in the aromatic series is considered necessary. This has been related to the metabolism of the o-methyl phenyl derivative to the cyclic phenyl saligenin phosphate (Craig & Barth, 1999; ACGIH, 2011). Whilst other mechanisms may lead to neurotoxicity, the lack of significant neurotoxic effects for the chemicals is supported by the available data.

The chemicals (TPCP and TMCP) did not inhibit hen brain neurotoxic esterase activity in vitro and there was no inhibition of brain neurotoxic esterase 24 hours after adult hens were treated with the chemicals at 1000 mg/kg (Sprague and Castles, 1985).

In an experiment to investigate the commercial product (TCP) and purified isomers (TOCP and TPCP) on axon outgrowth and neurofilament levels in mouse neuro-2a (N2a) neuroblastoma cells, TOCP inhibited the outgrowth of axon-like processes following exposure times of 24 h or longer. In contrast, TPCP demonstrated a transient effect on the outgrowth of axon-like processes, which was detectable after 24 but not 48 h of exposure (Fowler et al., 2001).

In another in vitro study with isolated cortical neurons TOCP significantly reduced the size and complexity of neurite networks, but neither TMCP and TPCP had any effects. The TMCP isomer was reported to have the lowest potency with respect to inducing neurotoxic effects (Hausherr et al., 2016).

Data for the structurally related chemical cresyl diphenyl phosphate (CAS No 26446-73-1) demonstrated isomer specific toxicity. In animals, cresyl diphenyl phosphate with o-cresyl phosphate content produced delayed polyneuropathy whereas the o-isomer free diphenyl cresyl phosphate had no similar effects (MAK, 2016; NICNASb).

Risk Characterisation

Critical Health Effects

Based on the available data, the critical health effects for risk characterisation include systemic long-term effects and reproductive toxicity. Unlike the ortho isomers of TCP, the chemicals are not considered to cause cause delayed neuropathy termed organophosphate-induced delayed neurotoxicity (OPIDN).

Public Risk Characterisation

Given the uses identified for these chemicals, 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 chemicals, although it is expected that the chemicals will be bound within the article or coated surface. Some of the chemicals 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). Therefore, the risks associated with exposure to the assessed chemicals is not considered to be unreasonable.

Occupational Risk Characterisation

During handling of the chemical, dermal and oral exposure of workers to these chemicals 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 chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. These chemicals 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) (refer to Recommendation section).

NICNAS Recommendation

Assessment of the chemical 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.

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.

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]

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)
Reproductive and Developmental Toxicity	Not Applicable	Suspected of damaging fertility - Cat. 2 (H361f)

[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 consumers

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

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;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

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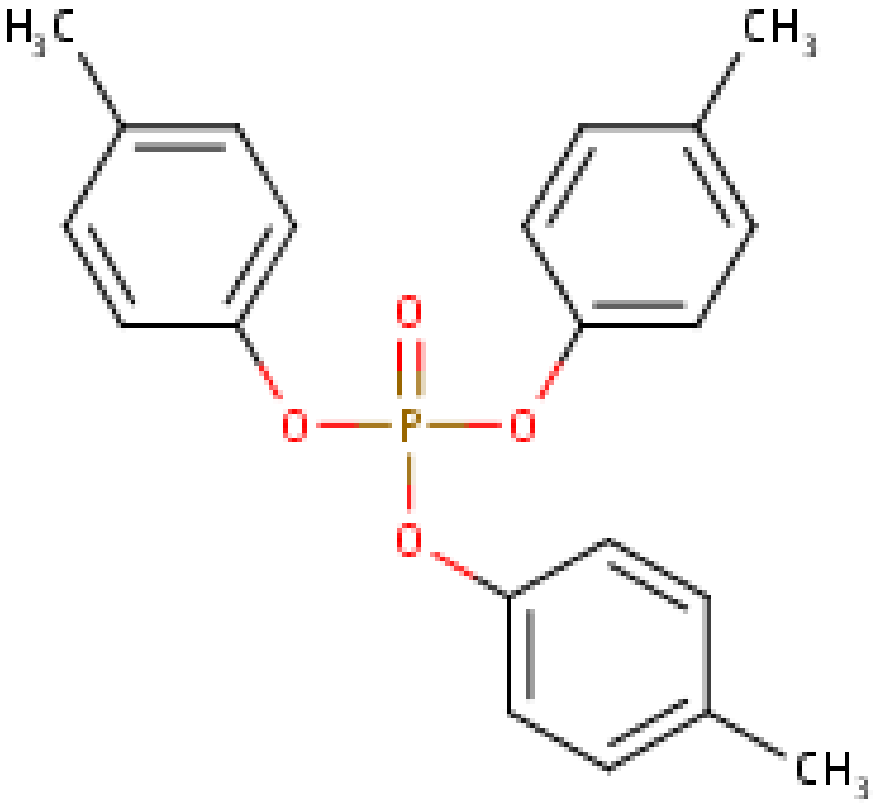
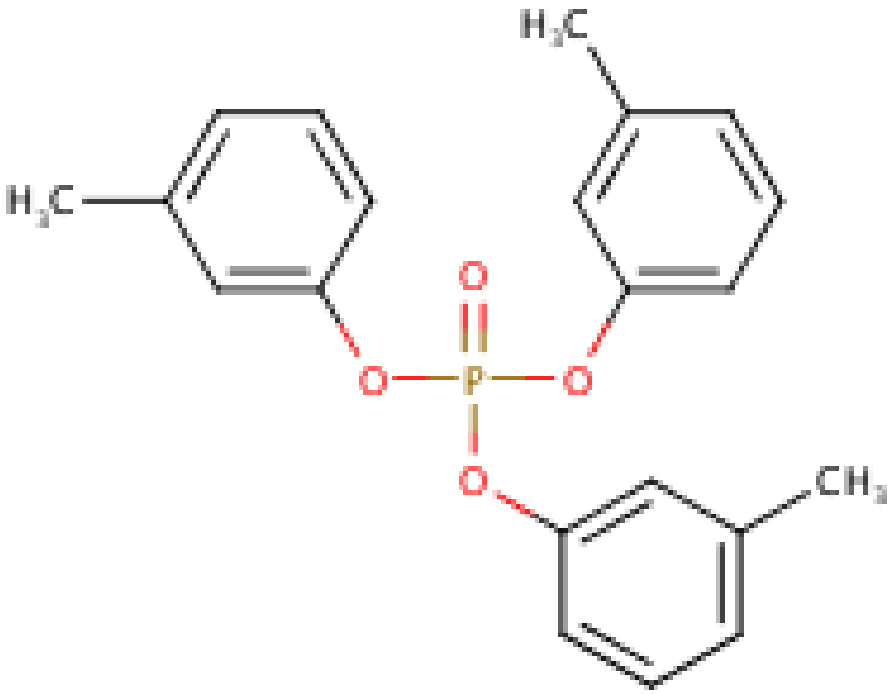
Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, tris(4-methylphenyl) ester** phosphoric acid, tri-p-tolyl ester TPCP tri-p-cresyl phosphate
CAS Number	78-32-0
Structural Formula	
Molecular Formula	C21H21O4P
Molecular Weight	

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, tris(3-methylphenyl) ester** phosphoric acid, tri-m-tolyl ester TMCP tri-m-cresyl phosphate
CAS Number	563-04-2
Structural Formula	

	
Molecular Formula	C21H21O4P
Molecular Weight	

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