Phosphoric acid, tris(methylphenyl) ester: Human health tier II assessment

02 March 2018

CAS Number: 1330-78-5

Preface

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

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

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

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

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

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

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted

and published separately, using information available at the time, and may be undertaken at different tiers.

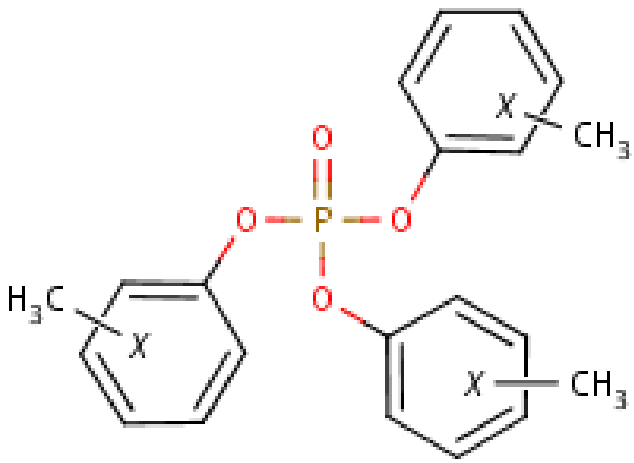
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	tricresyl phosphate cresyl phosphate tritolyl phosphate TCP
Structural Formula	
Molecular Formula	C21H21O4P
Molecular Weight (g/mol)	371.4
Appearance and Odour (where available)	Odourless viscous light yellow or transparent liquid.
SMILES	c1(OP(=O)(Oc2c(C)cccc2)Oc2c(C)cccc2)c(C)cccc1

Import, Manufacture and Use

Australian

The total volume introduced into Australia, reported under previous mandatory and/or voluntary calls for information was under 10 tonnes.

The following Australian industrial uses were reported 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 European Union Registration, Evaluation, Authorisation and Restriction of Chemicals (EU REACH) dossiers; Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) dictionary; the US National Library of Medicine's Hazardous Substances Data Bank (HSDB), and the World Health Organisation, International Program on Chemical Safety (WHO IPCS):

The chemical has reported possible domestic uses including in:

- adhesives;
- binding agents;
- corrosion inhibitors; and
- surface treatment products.

The chemical has reported commercial uses including:

- in hydraulic fluids and additives;
- in lubricants and additives;
- in softeners;
- in plastics;
- as a plasticiser; and
- as a lead scavenger in gasoline.

The chemical has reported site-limited uses including:

- as a chemical intermediate;
- as a laboratory reagent;
- as an additive in extreme pressure lubricants; and
- in non-flammable fluids in hydraulic systems.

The chemical also has a reported non-industrial use in non-agricultural pesticides and preservatives.

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following (Galleria Chemica):

- 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.

Existing Work Health and Safety Controls

Hazard Classification

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

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified (Galleria Chemica):

- an exposure limit of 0.1–0.5 mg/m^3 time weighted average (TWA) in Russia, China and South Africa; and
- a short-term exposure limit (STEL) of 0.3 mg/m^3 in South Africa.

Health Hazard Information

Phosphoric acid, tris (methylphenyl) ester, also commonly known as tricresyl phosphate (TCP), is an organophosphate used in numerous domestic, commercial and site-limited applications. In the past, the commercial product TCP consisted of a heterogeneous mixture that included three specific isomers; tri-o-cresyl phosphate TOCP) (CAS No. 78-30-8), tri-m-cresyl phosphate (CAS No. 563-04-2) and tri-p-cresyl phosphate (CAS No. 78-32-0).

The ortho-cresyl isomers are thought to be primarily responsible for the critical health effect of delayed organophosphate induced delayed neuropathy (OPIDN) (Winder & Balouet, 2002). Commercially produced TCP now contains minimal amounts of the TOCP.

Toxicokinetics

Absorption

The oral and dermal absorption of phosphoric acid, tris(methylphenyl) ester has been studied in a number of species. However, no information is available on its absorption via inhalation.

An early study demonstrated that this chemical (0.1 g/kg in olive oil) was absorbed orally in rabbits. Dermal absorption of TCP appears to differ markedly between species. A 1943 study demonstrated relatively poor dermal absorption in canines, while dermal absorption in humans is thought to occur approximately 100 times faster than in dogs (WHO, 1990). Another study reported that cats exhibit even greater absorption compared with dogs and humans, when administered [^{14}C]-tri-orthocresyl phosphate (TOCP) dermally, at a concentration of 50 mg/kg (Nomeir and Abou-Donia, 1984). The authors report that over 70 % of the applied TOCP disappeared from the cats' skin within 12 hours of application.

Distribution

The distribution of TCP has been assessed in several species. In one study, chickens were given a single oral dose of [^{32}P]-TCP (770 mg/kg). Total radioactivity in the liver rose consistently for 72 hours and was thought to be associated with the metabolites of TCP. The levels of radioactivity in the plasma were consistently lower than those in the liver and were associated with the unmetabolised form of TCP (Sharma and Watanabe, 1974).

In a study in which [^{32}P]-TCP (200 mg/kg) was administered to the abdominal skin of a dog, the radioactivity in the blood within 24 hours was equivalent to 80 µg/L. The chemical was distributed throughout the following tissues in descending order: liver, blood, kidney, lung, muscle and brain (Hodge and Sterner, 1943).

These studies, and others, suggest that tricresyl phosphate appears to be preferentially distributed to the liver.

Metabolism

This chemical is metabolised via three pathways:

1. one or more of the methyl groups can undergo hydroxylation, giving rise to mono- and di-hydroxymethyl TOCP (tri-*o*-cresyl phosphate, TMCP (tri-*m*-cresyl phosphate and TPCP (tri-*p*-cresyl phosphate) and (*o*, *m*, *p*)-hydroxybenzylalcohol;
2. the phosphate can be dearylated resulting in the formation (*o*, *m*, *p*)-cresol, di-(*o*, *m*, *p*)-cresyl phosphate, mono-(*o*, *m*, *p*)-cresyl phosphate and phosphoric acid; and
3. the hydroxymethyl groups can undergo further oxidation to give rise to aldehydes and carboxylic acids that result in the formation of mono-(or di-) cresyl di-(or mono-) carboxyphenyl phosphate and hydroxybenzoic acid.

Importantly, many species (including rats, rabbits, mice and chickens) metabolise ortho isomers of TCP to form a neurotoxic esterase inhibitor called saligenin cyclic o-tolyl phosphate [2-(o-cresyl)-4H-1:3:2-benzodioxaphos-phoran-2-one]. This metabolite could have significant implications for neurotoxicity in humans exposed to the chemical (WHO, 1990).

Excretion

Phosphoric acid, tris(methylphenyl) ester is excreted predominantly in urine and faeces, together with small amounts in exhaled breath. In a study carried out in hens, a single dose of [^{32}P]–TCP (770 mg/kg) was administered orally. Of the total radioactivity, 26.5 % was eliminated in the excreta over a period of 72 hours (Sharma and Watanabe, 1974).

In a study in male cats, approximately 28 % of the applied dose was excreted in the urine and 20 % via the bile into the faeces within 10 days (Nomeir and Abou-Donia, 1984).

Acute Toxicity

Oral

The chemical had low acute toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats is greater than 2000 mg/kg body weight.

In a non-guideline study, a commercial formulation of TCP was assessed for acute oral toxicity in Wistar-derived, adult albino rats. Animals were administered 20,000 mg/kg bw of test material in a single dose. During 14 days of observation, no deaths were recorded. Therefore, the LD50 of the test material under these conditions was found to be >20,000 mg/kg bw (IUCLID, 2001; REACHa).

Numerous other studies have been performed that support these findings. To summarise, the following oral LD50 values for tricresyl phosphate, expressed as mg/kg bw, have been reported:

- 5,190, >4,640 and >15,800 in rats;
- 3,900 in mice; and
- >10,000 in chickens (WHO, 1990).

Dermal

The chemical had low acute toxicity in animal tests following dermal exposure. The LD50 in rabbits is >2000 mg/kg bw.

TCP was assessed in a non-guideline dermal acute toxicity study using New Zealand White rabbits. Following pilot experiments to determine appropriate dose ranges, animals were split into groups and treated with the following concentrations of the chemical on abraded portions of their skin: 3140, 5000, 6300, 10000, or 12600 mg/kg bw. Animals were observed for signs of toxicity at one, three, six, and 24 hours post-dosing and were continually observed for a total of 14 days (REACHa). The study determined that the acute dermal toxicity of TCP (LD50) was 3700 mg/kg.

In another non-guideline study using albino rabbits, TCP was assessed for acute dermal toxicity at a single high dose of 10 g/kg. Following administration of the test material to the abraded skin of rabbits, no acute toxicity was observed. Therefore, under these test conditions, the TCP LD50 was reported as >10,000 mg/kg bw (IUCLID, 2001).

Two other experiments have assessed the acute toxicity of TCP via the dermal route. The TCP LD50 was found to be >7900 mg/kg bw and 1500 mg/kg bw in rabbits and cats, respectively (WHO, 1990).

Inhalation

Based on the available information the chemical has low acute toxicity following inhalation exposure.

A non-guideline study was conducted to assess the acute toxicity of TCP via inhalation in Sprague Dawley (SD) rats. The test material was aerosolised and delivered to the animals in a whole-body inhalation exposure chamber for one hour. The concentration of TCP was calculated to be 11.1 mg/L. Rats were observed for abnormal signs at 15-minute intervals throughout the exposure, and hourly for four hours following exposure. Monitoring continued for 14 days, after which rats were euthanised and necroscopy was performed (REACHa).

The exposure did not result in any mortalities. However, animals did exhibit a degree of agitation, consistent with pulmonary irritation. Necroscopy revealed some extent of pulmonary inflammation; however, few details were provided.

Under these test conditions, the chemical is not considered to be acutely toxic via inhalation.

Corrosion / Irritation

Skin Irritation

The chemical is not a skin irritant.

A commercial formulation of TCP (0.5 ml (0.5 g)) was applied to clipped areas of intact or abraded skin of New Zealand White rabbits and covered with occlusive patches. The animals were immobilised and patches removed after four hours. Application sites were assessed at four and 48 hours for erythema and oedema. Only mild irritation, which resolved after 24 hours, was observed (REACHa).

Another study assessed the dermal irritation response of adult albino rabbits to 0.5 mL (0.5 g) of a commercial formulation of TCP. This experiment followed the method outlined in the previous study; however, the chemical was left on the occluded skin for 24 hours. Under these test conditions, TCP was found not to cause dermal irritation (REACHa).

Eye Irritation

The chemical is not an eye irritant.

The potential for TCP to cause ocular irritation was assessed in a non-guideline study. In this study, 100 µL of test material was introduced to the right eye of nine New Zealand White rabbits. The effects of the chemical were assessed in both rinsed and unrinsed eyes. The cornea, iris, bulbar conjunctivae and palpebral conjunctivae were assessed for evidence of irritation or corrosion for seven days after treatment. Ocular instillation of 100 µL of undiluted chemical into the eyes of rabbits was slightly irritating with or without a four second ‘washout’ (REACHa).

Another study assessed a commercial formulation of TCP for its potential to cause eye irritation in adult albino rabbits. The conditions of this study, including time-course and dosing, mirrored those described in the previous experiment. Again, under these test conditions, the chemical was found to be only slightly irritating to the rabbit eye with or without a four second 'washout' (REACHa).

Sensitisation

Skin Sensitisation

A skin sensitisation study conducted using a local lymph node assay (LLNA) was inconclusive as stimulation indices (SI) >3, with no dose-response relationship, were found. A close structural analogue (triphenyl phosphate) of the chemical was found to be a non-sensitiser in a guinea pig maximisation test. Based on the results of this study, tricresyl phosphate is unlikely to act as a skin sensitiser.

The chemical was tested in an LLNA conducted according to OECD Test Guideline (TG) 429. In this study, CBA/J Rj mice were topically administered solutions containing the chemical at 25, 50 and 100 % on the dorsal surface of each ear. Animals were treated once a day for three consecutive days. Local lymph nodes were then assessed for incorporation of 3HTdR (tritiated thymidine), a measure of lymphocyte proliferation that is proportional to the sensitising effect of the test material. Stimulation index values of 3.7, 3.4 and 5.4 were calculated for applied concentrations of 25, 50 and 100 % of a commercial formulation of TCP, respectively. A stimulation index threshold value of at least three would normally be classified as a sensitiser. However, as the dose-response relationship was not clear, the findings of this study are difficult to interpret and ultimately inconclusive (REACHa).

Triphenyl phosphate (CAS No. 115-86-6) is a close structural analogue of tricresyl phosphate and its potential to act as a skin sensitiser is likely to mirror that of TCP. In an OECD TG 406 skin sensitisation study, triphenyl phosphate was evaluated using the guinea pig maximisation test. In this study, animals were injected intradermally with triphenyl phosphate together with an adjuvant. Seven days later, animals were treated topically with the test material at a concentration of 75 %. Fourteen days later, animals were challenged topically with triphenyl phosphate at 50 and 75 %. The skin was assessed for evidence of hypersensitivity 24 and 48 hours after the final treatment. The results of this study indicated that triphenyl phosphate produced a 0 % (0/10) sensitisation rate under these test conditions. This chemical is therefore considered not to be a skin sensitiser (REACHb).

Repeated Dose Toxicity

Oral

The weight of evidence suggests the chemical causes damage to health by prolonged exposure at a lowest observed adverse effect level (LOAEL) of 50 mg/kg bw/day. At this dose, the central nervous system (see ***Neurotoxicity*** section) and adrenal glands are adversely affected (see ***Recommendation*** section).

In one study, weanling SD rats were fed a diet containing 0.1, 0.5 or 1 % of the chemical for 28 days. Haematological examinations, clinical chemistry, urinalyses and faecal occult blood studies were performed on surviving animals, euthanised at the conclusion of the study (day 28). No toxicity was observed in the 0.1 % group; however, there were significant treatment-related toxic effects, including mortality (19/20 in the 1.0 % group; 9/20 in the 0.5 % group). Further, an increased liver to body weight ratio was observed in animals in the two higher dose groups at necropsy. The no observed effect level (NOEL) under these test conditions was 0.1 % TCP in the diet.

In another study, SD-SLC rats were exposed to TCP at 30, 100, 300 or 1000 mg/kg bw/day, once a day, six days a week, for three months. Parameters assessed included body weight, food and water intake, urinalysis, haematology, serum biochemistry and organ weights. The physiological changes seen in the animals were comparatively slight even in the highest dose group. No treatment-related mortalities occurred. Under these test conditions, the no observed adverse effect level (NOAEL) was assigned to the highest dose of 1000 mg/kg bw/day (REACHa).

In a United States National Toxicology Program (US NTP) repeated dose toxicity study, Fischer 344/N rats and B6C3F1 mice of both sexes (10/sex/dose) were administered TCP by gavage, five days a week for 13 weeks, at the following dose levels: 0, 50, 100, 200, 400 or 800 mg/kg bw/day. The study was well-documented and adhered to good laboratory practice (GLP). No mortalities were recorded during the study. The mean body weights were reduced in the higher dose groups. Multifocal neuronal degradation was reported in all groups (except the 50 mg/kg bw group) and degeneration of the sciatic nerves in the higher dose groups. Cytoplasmic vacuolisation of the adrenal cortex was observed in rats and mice of both sexes at all dose groups in a dose dependent manner. Effects in reproductive organs were also reported (see ***Reproductive and developmental toxicity*** section). An NOAEL was not identified in this study. The LOAEL under these test conditions, based on cytoplasmic vacuolisation of the adrenal cortex, was 50 mg/kg bw/day in both sexes of both rats and mice (REACHa; Government of Canada, 2016).

In a dietary 13-week repeated dose toxicity study, Fischer 344/N rats and B6C3F1 mice of both sexes (10/sex/dose) received diets containing TCP. The male rats received approximately 0, 55, 120, 220, 430 or 750 mg/kg bw/day and female rats received 65, 120, 230, 430 or 770 mg/kg bw/day of TCP. The male mice received approximately 0, 45, 110, 180, 380 or 900 mg/kg bw/day and female mice received 0, 65, 130, 230, 530 or 1050 mg/kg bw/day of TCP. No mortalities were reported during the study. The mean body weights were significantly decreased in male rats at 430 mg/kg bw/day and higher, and in female rats at 230 mg/kg bw/day and higher. Cytoplasmic vacuolisation of the adrenal cortex was observed in all exposed rats and mice except for the male mice treated at the lowest dose group. Effects in reproductive organs were also reported (see ***Reproductive and developmental toxicit***y section). The NOAEL for male mice was 45 mg/kg bw/day. NOAELs for rats and female mice were not determined.

Numerous other studies have assessed TCP for repeated dose toxicity. In another 90-day oral gavage study on rats, a LOAEL, again based on cytoplasmic vacuolisation of the adrenal cortex, was established as 50 mg/kg bw/day in both sexes of animals (REACHa).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

There are numerous reports of TCP poisoning in humans, typically associated with ingesting contaminated foodstuffs.

Short-term manifestations of TCP poisoning can include emesis, abdominal pain and diarrhoea. The distinctive neurological signs of poisoning are delayed in onset and include paralysis and issues relating to damage to the pyramidal tracts. This type of poisoning is typical of organophosphates and is often referred to as organophosphate-induced delayed neuropathy (Lotti & Moretto, 2005).

Oral

In 1930, 50000 people in America were exposed to TCP after consuming a substitute for alcohol called ‘Ginger Jake’, made popular during prohibition (Morgan, 1982). Later analysis of the liquid revealed the presence of TOCP at a concentration of 2 %. Numerous incidences of paralysis were reported.

In 1959, approximately 10000 people in Morocco were exposed to the TOCP isomer after cooking oil became contaminated with jet engine oil.

Dermal

A 1943 paper reported the case of a worker who developed symptoms consistent with neurotoxicity after being exposed to TOCP over a period of two years in a German chemical plant. The route of exposure was deemed to be via percutaneous absorption (WHO, 1990).

Inhalational

A 1944 study reported the occupational exposure of workers to TCP in a manufacturing facility in England. These subjects developed polyneuropathy as a result of skin and inhalational absorption of the chemical (Hunter et al., 1944).

These reports of TCP poisoning largely focus on the TOCP isomer. Although the data are not quantifiable in terms of repeated dose toxicity, it is clear that the chemical poses a risk to human health.

Genotoxicity

Based on the available in vitro studies, TCP is not expected to be genotoxic.

In vitro studies

In a study conducted similarly to OECD TG 471 (bacterial reverse mutation assay), five bacterial strains (*Salmonella typhimurium* TA 1535, TA 1537, TA1538, TA 98 and TA 100) were exposed to TCP at the following concentrations: 0.00001, 0.0001, 0.001, 0.01 and 0.1 mg/L. No mutagenicity was observed at any of the concentrations assessed, either in the presence or absence of metabolic activation (REACHa).

In well-characterised chromosomal aberration and sister chromatid exchange assays, TCP was found not to be genotoxic at concentrations of 0.00063, 0.00125, 0.00250, 0.00500 and 0.0100 µL/ml both with and without metabolic activation, using a mouse lymphoma cell line.

In another in vitro study carried out in accordance with OECD TG 473 (in vitro mammalian chromosome aberration test) the chemical was tested at concentrations of 1.37, 4.12, 12.35, 37.04, 111.1, 333.3 or 1000 µg/ml in cultured V79 Chinese hamster lung fibroblasts. Treatment with the chemical did not result in a statistically or biologically significant dose-dependent increase in the frequency of the cells with structural chromosome aberrations either in the presence or absence of metabolic activation at any dose. Therefore, under these conditions, TCP was not genotoxic (REACHa).

In vivo studies

No in vivo studies were identified.

Carcinogenicity

The chemical was considered not to be carcinogenic based on two studies undertaken in rats and mice.

In one study, groups of 95 male and 95 female Fischer 344 (F344) rats were fed diets containing 0, 75, 150, 300 or 600 ppm of TCP (equivalent to approximately 0/0, 3/4, 6/7, 13/15 or 26/30 mg/kg bw for males/females, respectively). After three, nine, 15 and 24 months of exposure, up to 15 animals per group were assessed for limb grip strength and were euthanised for necroscopic evaluation. Mean body weights and food intake were also assessed (IUCLID, 2001). Survival rates, mean body weights and food intake were similar across all groups and controls. There were no chemical-associated increases in the incidence of neoplasms in test animals. Therefore, under these test conditions, TCP was not considered carcinogenic.

A second study was conducted under GLP (REACHa). Groups of 95 male and 95 female B6C3F1 mice were fed diets containing 0, 60, 125, or 250 ppm of TCP (equivalent to approximately 0/0, 7/8, 13/18 or 27/37 mg/kg bw for males/females, respectively). After three, nine, 15 and 24 months of exposure, up to 15 animals per group were evaluated for limb grip strength and were euthanised for necroscopic evaluation. Survival rate, mean body weight and food intake were similar across all groups and controls. No chemical-related increase in the incidence of neoplasms was noted. Therefore, under these test conditions, TCP was not considered carcinogenic.

Reproductive and Developmental Toxicity

The chemical is toxic to reproduction. Based on the reproductive effect outcomes together with histological changes in reproductive organs in rats, classification for reproductive toxicity is warranted (see ***Recommendation*** section).

Reproductive toxicity

TCP was assessed in a non-guideline one-generation reproductive toxicity study (REACHa). Male Long Evans rats were administered 0, 100 or 200 mg/kg bw/day and females 0, 200 or 400 mg/kg bw/day TCP by gavage. Males from the 100 mg/kg bw/day group were mated with the 200 mg/kg bw/day females, and the 200 mg/kg bw/day males were bred with females from the 400 mg/kg bw/day group. Males were dosed for 56 days and females for 14 days before breeding and throughout the 10-day breeding period. Following breeding, males were euthanised and assessed for sperm parameters and reproductive histopathology. Females were administered the chemical throughout gestation and lactation. Adults and pups were euthanised and necroscopied on postnatal day 21.

Sperm concentration, motility, and progressive movement were decreased in male rats at 200 mg/kg bw/day. A dose-dependent increase in abnormal sperm morphology was observed in the males from both treatment groups. Significant histopathological changes were observed in the testes of male rats at 200 mg/kg bw/day and in the ovaries of female rats at 400 mg/kg bw/day. The number of female rats that delivered pups after TCP exposure was decreased at both doses tested (9/24 and 1/24 at 200 and 400 mg/kg bw/day, respectively, compared with 22/24 in control females). Litter size and pup survival were decreased in the 400 mg/kg bw/day group. Pup body weight and developmental parameters were unaffected by TCP exposure. A NOAEL was not identified in this study (REACHa).

A non-guideline continuous breeding study was conducted in Swiss (CD1) mice using mixed TCP isomers (in the diet) at doses equivalent to 62.5, 124 or 250 mg/kg bw/day. TCP induced functional and structural effects in the male reproductive system and functional reproductive impairment in females. Effects on fertility were observed at doses of 124 mg/kg bw/day or higher. Reproductive pathologies in males included seminiferous tubule atrophy, and decreased testicular and epididymal weights from the lowest dose group. Sperm motility was reduced in both the 62.5 mg/kg bw/day and 124 mg/kg bw/day groups compared with controls. The LOAEL for reproductive toxicity of TCP was found to be 62.5 mg/kg bw/day.

In a US National Toxicology Program (NTP) oral repeated dose toxicity study, Fischer 344/N rats and B6C3F1 mice of both sexes were administered 0, 50, 100, 200, 400 or 800 mg/kg bw/day of TCP by gavage, five days a week for 13 weeks (for more details see ***Repeated dose toxicity*** section). Ovarian interstitial cell hypertrophy was observed in all treated female rat and mouse groups. Atrophy of the testicular seminiferous tubules was observed in male rats at doses of 400 mg/kg bw/day and higher (Government of Canada, 2016).

In a dietary 13-week repeated dose toxicity study, Fischer 344/N rats and B6C3F1 mice of both sexes (10/sex/dose) received diets containing TCP. Ovarian interstitial cell hypertrophy and inflammation of the ovarian interstitium were observed in all female rat groups receiving TCP in diet. Basophilic hypertrophy of the pituitary and atrophy of the testicular seminiferous tubules were reported at 430 mg/kg bw/day and higher dose in male rats. The LOAEL for the effects in reproductive organs was 55 mg/kg bw/day based on ovarian effects in female rats (Government of Canada, 2016).

In another non-guideline study, the TOCP isomer was administered to SD rats at 150 mg/kg bw/day for periods of 3, 7, 10, 14 or 21 days; numerous reproductive toxicity parameters were assessed. Sperm motility and numbers were reduced in exposed animals by following dosing for 10 days. Testicular weight to body weight ratio was significantly decreased in animals treated for 21 days. Sex hormone levels were normal after exposure in all groups. Sertoli cell fluid secretion showed no significant changes. A separate group of animals was treated for 21 days and subjected to pathological examination after 98 days of observation. Irreversible damage to the process of spermatogenesis was observed. This study only assessed one isomer of TCP and, as a result, may overstate the reproductive toxicity potential of TCP (REACHa).

Developmental toxicity

In a developmental toxicity study conducted similar to OECD guidelines, SD rats were administered TCP on gestation day 0–19, at concentrations of 20, 100, 400 or 750 mg/kg bw/day. Developmental toxicity was assessed in both adult females and their pups. Under these test conditions, the TCP NOAEL for maternal toxicity was 20 mg/kg bw/day. Maternal toxicity manifested as an increase in the frequency of salivation in the 100 mg/kg bw group and as a loss of hair and unkempt appearance in the two highest dose groups. Lower body weights were seen at 400 and 750 mg/kg bw/day and reduced food consumption was seen at 750 mg/kg bw/day. Lower foetal body weights were seen at all dose levels. However, the changes at 20, 100 and 400 mg/kg bw/day dose groups were not of biological significance, with differences reported of 4.4 to 9 % compared with the control animals. Foetal skeletal examination suggested impaired or delayed ossification in the highest dose group. It appears that the lower foetal body weights are secondary to maternal toxicity (REACHa).

Other Health Effects

Neurotoxicity

A neurotoxicology assessment was performed using a commercial formulation of TCP in hens. The study was not conducted in compliance with any recognised test guidelines and the results could be confounded due to a change in the constituents of the test material. More recently, commercial TCP is produced with minimal amounts of the TOCP isomer, which has been particularly associated with inducing delayed neuropathy.

In this study, the chemical was assessed for neurotoxicity from oral exposure when administered at 75, 150 or 300 mg/kg bw/day, and from dermal exposure at a dose of 50 mg/kg bw/day. Oral doses were administered via gastric intubation and the dermal dose was applied to the highly vascularised combs and wattles of the hens. The test material produced a clinical response in the 75–300 mg/kg bw oral dose range. The commercial formulation of TCP also elicited a clinical neurotoxic response within 29–38 days when applied dermally at 50 mg/kg per day, five days a week. Due to the age of this study (performed in 1977) and the subsequent changes made to commercially produced TCP, the results of this study might not represent current TCP use (REACHa).

Another commercial formulation of TCP was assessed in a more recent study, conducted in compliance with the US Environmental Protection Agency (EPA) guideline for acute and 28-day delayed neurotoxicity of organophosphorus substances. Undiluted test material was administered as a single dose of 2000 mg/kg bw, to adult hens. Based on the results of this study, oral administration of test material at 2000 mg/kg did not result in any adverse histological changes (REACHa).

In another non-guideline study, TCP was assessed for neurotoxicity in adult hens. Animals were administered the chemical as a 3 % solution in synthetic polyol-based oil by gavage, five days a week for 13 weeks. Clinical, biochemical and neuropathological

endpoints were assessed. The results suggest that TCP exhibited low neurotoxic potential and should not pose a hazard at the expected levels of exposure to humans (REACHa).

A well documented 2004 non-guideline study assessed the sublethal neurotoxic effects of TCP and its isomers on differentiating mouse N2a neuroblastoma cells. Several parameters were evaluated including cell viability, axonal outgrowth as well as the levels of cytoskeletal proteins present (an indicator of neuronal health). TCP was found to inhibit axonal outgrowth following exposure for 24 hours or longer. These experiments also indicated that TCP and TOCP exhibited similar levels of toxicity to cells following both the 24-hour and 48-hour exposure. Isomer-specific patterns of toxicity were also evident, with only the ortho isomer showing significant levels of inhibition of axon outgrowth following 48 hours of exposure.

The investigators also reported that neuroblastoma cells exhibited an exaggerated response to TOCP in the presence of metabolic activation, as indicated by a further increase in the inhibition of axonal outgrowth. This finding suggests that the TOCP isomer can be converted into a more toxic metabolite. These experiments, therefore, provide evidence that indicates that the TOCP isomer and its metabolites have a greater potential to induce neurotoxicity than the other TCP isomers (REACHa).

Two separate studies, performed in the same laboratory (referred to in the carcinogenicity section of this report), assessed the effect of repeated oral exposure to TCP containing <0.1 % of TOCP.

In one study, groups of 95 male and 95 female F344 rats were fed diets containing 0, 75, 150, 300 or 600 ppm of TCP (equivalent to approximately 0/0, 3/4, 6/7, 13/15 or 26/30 mg/kg bw for males/females, respectively). The chemical formulation contained <0.1 % TOCP. Significantly decreased hind limb grip strength was reported for male rats at the two highest treatment levels (13 and 26 mg/kg bw) and for female rats at the highest treatment level (30 mg/kg bw) at three months. No such effects were observed at 9 and 15 months. These findings suggest some form of transient neurotoxicity occurred; however, it alone is not enough to warrant classification (REACHa; US EPA, 2014).

In the second of these studies, groups of 95 male and 95 female B6C3F1 mice were fed on diets containing 0, 60, 125, or 250 ppm of TCP (equivalent to approximately 0/0, 7/8, 13/18 or 27/37 mg/kg bw for males/females, respectively). At the three-month interim evaluation, investigators reported significantly decreased hind limb grip strength in female mice of the highest treatment level (250 ppm); there was no significant change in this parameter at 9- and 15-month interim evaluations. Again, these findings suggest some form of transient neurotoxicity occurred; however, this result alone is not enough to warrant classification (US EPA, 2014; REACHa).

In a repeated dose toxicity study (see ***Repeated dose toxicity*** section), B6C3F1 mice of both sexes were administered TCP by gavage, five days a week for 13 weeks at the following concentrations: 0, 50, 100, 200, 400 or 800 mg/kg bw/day. No mortalities were recorded during the study; however, neurotoxic abnormalities were observed, including multifocal neuronal degradation in all groups (except the 50 mg/kg body weight group) as well as degradation of adrenal cortices and degeneration of the sciatic nerves in higher dose groups (REACHa).

The evidence provided here suggests that the TOCP isomer of TCP presents a significant risk of neurotoxicity. However, because commercially available TCP is now typically produced with very low amounts of the TOCP isomer, the risk associated with exposure to the test material may be less significant than in the past.

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include a systemic long-term effect (reproductive toxicity) and, depending on the precise composition, neurotoxicity. The chemical can also cause toxic effects following repeated exposure through ingestion.

Public Risk Characterisation

Given the limited introduction volume and site-limited uses identified for the chemical, it is unlikely that the public will be exposed. Hence, the public risk from this chemical is not considered to be unreasonable.

Occupational Risk Characterisation

During handling of the chemical, dermal, oral and inhalation exposure of workers to the chemical 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 systemic long-term health effects, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise dermal and inhalation exposure are implemented. The chemical 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 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.

The neurotoxic effects of this chemical appear to relate to the relative concentration of the TOCP isomer in product formulations. Modern formulations with minimal levels of TOCP contaminants are less likely to be neurotoxic and, if the relevant formulation can be demonstrated to be non-neurotoxic, the GHS H370 classification may not be required.

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	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 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 which may 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 chemical 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 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 assist with meeting 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.

References

American Conference of Governmental Industrial Hygienists (ACGIH), 2011. Documentation of the Threshold Limit Values for Chemical Substances, ACGIH Signature Publications, 7th Edition.

Barratt, M. D.,& Langowski, J. J. (1999). Validation and subsequent development of the DEREK skin sensitization rulebase by analysis of the BgVV list of contact allergens. Journal of chemical information and computer sciences, 39(2), 294-298.

CosIng. Cosmetic Ingredients and Substances. Accessed November 2014 at http://ec.europa.eu/consumers/cosmetics/cosing/.

Craig PH and Barth ML, 1999. Evaluation of the hazards of industrial exposure to tricresyl phosphate: a review and interpretation of the literature. J of Toxicol Environ Health, Part B. 2, 281-300.

Craig, P. H., & Barth, M. L. (1999). Evaluation of the hazards of industrial exposure to tricresyl phosphate: a review and interpretation of the literature. Journal of Toxicology and Environmental Health Part B: Critical Reviews, 2(4), 281-300.

Galleria Chemica. Accessed October 2014 at https://jr.chemwatch.net/galleria/

Globally Harmonised System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third edition. Accessed at http://www.unece.org/trans/danger/publi/ghs/ghs_rev03/03files_e.html

Government of Canada (2016). Draft Screening Assessment. Certain Organic Flame Retardants Substance Grouping. Phosphoric acid, tris(methylphenyl) ester (TCP). CAS No 1330-78-5. Accessed February 2018 at http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=B356BCC9-1

Hodge, H. C., & Sterner, J. H. (1943). The skin absorption of triorthocresyl phosphate as shown by radioactive phosphorus. Journal of Pharmacology and Experimental Therapeutics, 79(3), 225-234.

Hunter, D., Perry, K. M., & Evans, R. B. (1944). Toxic polyneuritis arising during manufacture of tricresyl phosphate. British journal of industrial medicine, 1(4), 227.

International Uniform Chemical Information Database (IUCLID) 2001. Dataset. Tricresyl Phosphate (1330-78-5). Accessed October 2014 at http://www.epa.gov/chemrtk/pubs/summaries/tricphos/c13318rs.pdf

Lotti, M., & Moretto, A. (2005). Organophosphate-induced delayed polyneuropathy. Toxicological reviews, 24(1), 37-49.

Morgan, J. P. (1982). The Jamaica ginger paralysis. Journal of the Americal Medical Association, 248(15), 1864-1867.

Nomeir, A. A., & Abou-Donia, M. B. (1984). Disposition of [14C] tri-o-cresyl phosphate and its metabolites in various tissues of the male cat following a single dermal application. Drug metabolism and disposition, 12(6), 705-711.

REACH Dossier. Triphenyl phosphate (CAS No. 115-86-6) (REACH). Accessed November 2014 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

REACH Dossier. Tris(methylphenyl) phosphate (CAS No. 1330-78-5) (REACH). Accessed October 2014 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Safe Work Australia. Hazardous Chemicals Information System (HCIS). Accessed February 2018 at http://hcis.safeworkaustralia.gov.au/HazardousChemical

Sharma, R. P., & Watanabe, P. G. (1974). Time related disposition of tri-o-tolyl phosphate (TOTP) and metabolites in chicken. Pharmacological research communications, 6(5), 475-484.

Sjogren B, Iregren A, and Järnberg J, 2010. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. 143. Phosphate triesters with flame retardant properties. Nr 2010; 44(6). University of Gothenburg.

Substances in Preparations in Nordic Countries (SPIN). Accessed October 2014 at http://195.215.202.233/DotNetNuke/default.aspx

U.S. Environmental Protection Agency (EPA) Design for the Environment (2014). Flame Retardants used in Flexible Polyurethane Foam: An Alternatives Assessment Update. Accessed November 2014 at http://www.epa.gov/dfe/pubs/projects/flameret/ffr-update-complete.pdf

US Department of Health and Human Services, Household Products Database (HHPD), health and safety information on household products. Accessed October 2014 at http://householdproducts.nlm.nih.gov/

US National Library of Medicine's Hazardous Substances Data Bank (HSDB). Tricresyl phosphate (CAS No. 1330-78-5). Accessed November 2014 at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB

Winder C and Balouet J-C, 2002. The toxicity of commercial jet oils. Environ Res 89(2):146-64.

World Health Organisation (WHO) 1990. International Programme on Chemical Safety (IPCS) Environmental Health Criteria 110 - Tricresyl Phosphate. Accessed October 2014 at http://www.inchem.org/documents/ehc/ehc/ehc110.htm#PartNumber:7

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