2-Propanol, 1,3-dichloro-, phosphate (3:1): Human health tier II assessment

02 March 2018

CAS Number: 13674-87-8

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.

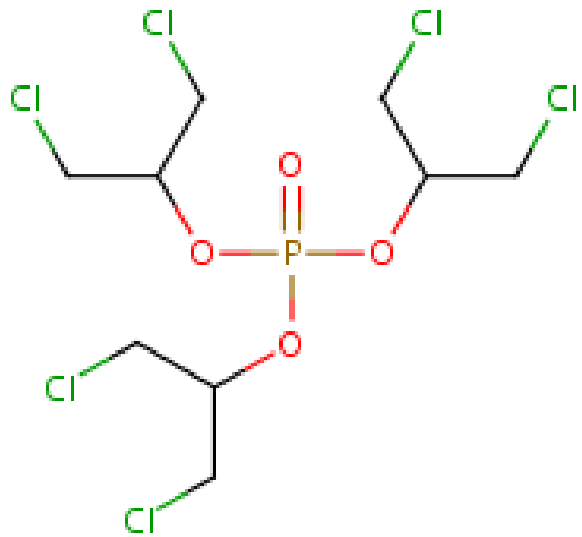
This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

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

Disclaimer

Acronyms & Abbreviations

Chemical Identity

Synonyms	tris(1,3-dichloro-2-propyl) phosphate TDCPP TDCP 1,3-dichloro-2-propanol phosphate (3:1) Fyrol FR 2
Structural Formula	
Molecular Formula	C9H15Cl6O4P
Molecular Weight (g/mol)	430.89
Appearance and Odour (where available)	Clear colourless viscous liquid. Mild odour.
SMILES	C(CCl)(CCl)OP(=O)(OC(CCl)CCl)OC(CCl)CCl

Import, Manufacture and Use

Australian

The following Australian uses have been identified through websites, safety data sheets (SDSs) available in Australia, and Triphosphates Priority Existing Chemical Assessment Report No. 17 (NICNAS, 2001):

The chemical may have domestic and commercial uses as a flame-retardant and/or plasticiser in:

- manufacture of flexible and rigid foams;
- manufacture of elastomers and specialist rubber materials;
- fibreglass resins and other moulded objects;
- surface coatings such as sealants and industrial paints; and
- interior cable coatings.

International

The following international uses have been identified through the Agency for Toxic Substances and Disease Registry Toxicological Profile for Phosphate Ester Flame Retardants (ATSDR, 2012); Environment and Climate Change Canada (Environment and Climate Change Canada, 2016); the European Union Risk Assessment Report (EU RAR, 2008); the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB); the US National Toxicology Program (NTP); the Organisation for Economic Co-operation and Development Screening information data set Initial Assessment Profile (OECD SIAP, 2009); the Substances and Preparations in Nordic countries (SPIN) database; the Environmental Protection Agency (US EPA) Flame Retardants Used in Foam An Alternative Assessments Update (US EPA, 2015); and the US EPA Toxic Substances Control Act (TSCA) Work Plan Chemical Problem Formulation and Initial Assessment (US EPA TSCA, 2015).

The chemical has reported commercial uses:

- as a flame retardant;
- as a plasticiser;
- in flexible and rigid polyurethane foams;
- in plastics; resins; and fabric backings;
- in extinguishing agents;
- as a binder for water colours;
- as a hardener in resins;
- as a solvent for hard resins and nitrocellulose; and
- as a cement for celluloid.

The chemical has reported site-limited uses in the manufacture of:

- machinery, vehicles, and furniture; and
- photographic and cellulose lacquer.

The chemical is used as a flame retardant and/or plasticisers in articles with domestic use including:

- upholstered furniture and bedding;
- baby products;
- automotive seating, fabrics, and roofing;
- lacquer, paint, and glue; and
- building/construction materials (laminates, pipes, ducts).

Restrictions

Australian

No known restrictions have been identified.

International

The chemical is listed on the following:

- Canada List of Prohibited and Restricted Cosmetic Ingredients (The Cosmetic Ingredient “Hotlist”) (Galleria Chemica);
- EU REACH Regulation (EC) No 1907/2006: Annex XVII. Restrictions on the manufacture, placing on the market and use of certain dangerous substances, mixtures and articles (Galleria Chemica);
- The European Commission—Commission directive 2014/79/EU of 20 June 2014, amending Appendix C of Annex II to Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys. Limit value of 5 mg/kg (content limit) for use in toys intended by children under 36 months or in other toys intended to be placed in the mouth (The European Commission, 2014);
- Commonwealth of Massachusetts—An Act to protect children and families from harmful flame retardants, S. 2293. Prohibits the sale of children's products and residential upholstered furniture that contain more than 1000 ppm of TDCPP (as of January 1, 2017) (Commonwealth of Massachusetts, 2016);
- District of Columbia—Carcinogenic Flame Retardant Prohibition Amendment Act of 2016. No person or legal entity shall manufacture, sell, offer for sale, or distribute any children's product or residential upholstered furniture containing more than 0.1 % TDCPP by mass (as of January 1, 2019) (District of Columbia, 2016);
- State of Washington—An Act relating to reducing public health threats that particularly impact highly exposed populations, including children and firefighters, but establishing a process for the department of health to restrict the use of toxic flame retardant chemicals in certain types of consumer products — No one may manufacture, sell, offer for sale, or distribute for use in that state any children’s products or residential upholstered furniture that contain TDCPP in amounts greater than 1000 parts per million (as of July 1, 2017) (State of Washington, 2016); and
- The United States Consumer Product Safety Commission (US CPSC) has initiated the rulemaking process under the Federal Hazardous Substances Act (FHSA) to ban the use of organohalogen flame retardants in an additive form in several consumer product categories including children's products, upholstered residential furniture, mattresses and the external casings of electronics devices (US CPSC, 2017).

Existing Work Health and Safety Controls

Hazard Classification

The chemical is classified as hazardous, with the following risk phrase for human health in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia):

- Carcinogenicity Category 2, H351 (Suspected of causing cancer).

Exposure Standards

Australian

No specific exposure standards are available.

International

No specific exposure standards are available.

Health Hazard Information

Toxicokinetics

Experimental data

The chemical is rapidly absorbed and extensively distributed following oral and dermal exposure. The highest levels of chemical are reported in the kidney, liver, and lung, following oral, dermal or intravenous administration. The chemical is rapidly and extensively (100 %) metabolised to bis(1,3-dichloro-2-propyl)phosphate (BDCPP; CAS No. 72236-72-7) and rapidly excreted, mainly via the urine (ATSDR, 2012; US EPA TSCA, 2015; REACH). Hydrolysis to BDCPP is presumed to result in production of 1,3-dichloro-2-propanol, previously assessed under IMAP (CAS No. 96-23-1).

In a non-guideline study, intestinal absorption and distribution of radioactively labelled ^{14}C-TDCPP were examined in male Sprague-Dawley (SD) rats (at least 3 animals per treatment). Rats were orally administered 0.2, 2 and 20 µmol/kg bw of TDCPP (86 µg/kg bw, 860 µg/kg bw and 8.6 mg/kg bw, respectively). Within 24 hours, over 90 % of the administered dose was adsorbed from the gastrointestinal tract. The tissue distribution pattern after 24 hours, in decreasing order based on concentration, was kidney > liver > lung > blood > muscle. More than 80 % of the administered dose was excreted within the first 24 hours, in urine, faeces, or expired as carbon dioxide (Nomeir et al., 1981; EU RAR, 2008; ATSDR, 2012; Environmental and Climate Change Canada, 2016; REACH).

In the same study, the intravenous and dermal routes were also examined. Dermal adsorption was examined by applying ^{14}C-TDCPP (0.867 mg/kg in a 60 µL methanol solution) to the shaved dorsal skin (area of 4 cm^2) of male SD rats (at least 3 animals) for 4 hours. The chemical was rapidly (rate not reported) absorbed through rat skin.

Fifteen minutes after intravenous administration of ^{14}C-TDCPP (2 µmol/kg bw, 0.867 mg/kg bw), the highest concentrations of radioactivity were reported in the lung followed by liver, kidney and blood. The higher concentration in the lung is possibly due to a first pass effect resulting from intravenous administration. Following 7 hours post exposure, the radioactivity was decreased in most tissues (except skin). A marked decrease was observed in all tissues by 24 hours. By day 10, radioactivity was only 1–5 % of that observed 15 minutes post-exposure.

The metabolites recovered from rat urine following intravenous administration were BDCPP (67.2 % of total urine radioactivity), an unidentified polar metabolite (32 %), 1,3-dichloro-2-propyl phosphate (0.29 %) and un-metabolised TDCPP (0.45 %). The chemical was shown to be metabolised by a NADPH-dependent microsomal mixed-function oxidase system and a glutathione-dependent transferase system in vitro (Nomeir et al., 1981).

The chemical was rapidly excreted following intravenous administration, with a 90 % decrease in radioactivity recorded in all tissues within the first 24 hours. The total radioactivity excreted after 24 hours was 34 %, 20 % and 20 %, in the urine, faeces and expired air, respectively. Excretion of the administered dose was 27 % in the bile, within 4 hours. Within 10 days after administration, approximately 47 % and 21 % of the total TDCPP dose was excreted in the urine and faeces, respectively. The half-life of TDCPP clearance in tissues was between 1.5–5.4 hours depending on the tissue (Nomeir et al., 1981; EU RAR, 2008; Environment and Climate Change Canada, 2016). Due to the rapid elimination of the chemical, no accumulation in the body is expected (US EPA, 2015).

In a non-guideline study, 5 male Wistar rats were orally administered 50 µmol/kg bw ^{14}C-TDCPP in olive oil (corresponding to 21.5 mg/kg bw). An additional 5 male rats were given a single oral dose of 50 µmol/kg ^{14}C-TDCPP. After one week, the recovery of radioactivity was 43.2 % in urine, 39.2 % in faeces, 16.2 % in expired air and 2.5 % in carcass. Approximately 40 % of administered radioactivity was excreted via the bile. The average Tmax value (average time at which TDCPP reached the maximum concentration in the tissue) for TDCPP radioactivity in blood and tissues was 9.6 hours. Tissue/blood ratios over 7 days were >1 for liver and kidney tissues, which indicates incorporation of radioactivity into these tissues. The decrease in radioactivity in all tissues was biphasic. The longest half-time was recorded in adipose tissue in both phases of elimination. However, the concentration in adipose tissue was low, suggesting lack of bioaccumulation. The biliary/faecal excretion ratio was 1.04 at 48 hours, implying there was no enterohepatic recirculation from the gastrointestinal tract (Minegishi et al., 1987; EU RAR, 2008; REACH).

In an in vitro percutaneous absorption study, dermal absorption was determined using human skin membranes. Following the topical application of ^{14}C-TDCPP for 8 hours of exposure (mimicking a normal working day), the mean total absorption was 15.4 %, 10.7 % and 6.0 % for doses of 0.003, 0.01 and 0.12 mg/cm^2, respectively (EU RAR, 2008; OECD SIAP, 2009; REACH).

In an in vitro flow-through diffusion cell study, ^{14}C-TDCPP in acetone (concentrations of 20, 100, or 200 pmol) was applied to dorsal skin discs from adult hairless mice. The receptor fluid was collected over 24 hours, after which the skin was washed with ethanol to remove unabsorbed TDCPP. The 24-hour cumulative percentage of the dose in the receptor fluid was 57 %, 45 % and 39 % for the 20, 100, and 200 pmol concentrations, respectively. The greatest percentage of the dose was absorbed between 6–12 hours for all concentrations. Following washing with ethanol, 28–35 % of the applied radioactivity remained in the skin. The metabolism of TDCPP in skin at the highest concentration appeared to be very small, if at all (ATSDR, 2012; REACH).

In a chronic study, adult zebrafish were exposed to 0, 40, 20 and 100 µg/L of TDCPP for 3 months. The chemical was detected in F1 eggs following parental exposure, indicating maternal transfer (Wang et al., 2015a; Environment and Climate Change Canada, 2016).

Human data

The chemical was detected in adipose tissue and seminal fluid from members of the general population, suggesting that TDCPP is absorbed into the body (ATSDR, 2012).

The chemical has been detected in mothers' milk in Sweden (4.3 ng/g lipid median weight (range of 1.6–5.3 ng/g lipid weight)) (Sundkvist et al., 2010) and Japan (range of non-detectable to 162 ng/g lipid weight) (Kim et al., 2014).

The primary metabolite BDCPP was determined in urine of 29 (100 %) adult office workers at a geometric mean (GM) concentration of 408 pg/mL (range of 62.1–1760 pg/mL). This demonstrates that TDCPP is entering and being metabolised in humans. TDCPP was also measured in dust collected from homes, vehicles, and offices of these workers suggesting that exposure to TDCPP in these environments are contributors to the exposure. The possible pathways of exposure include inhalation and dermal pathways (Carignan et al., 2013).

Acute Toxicity

Oral

The chemical has low acute toxicity following oral exposure. The reported oral median lethal dose (LD50) in rats is >2000 mg/kg bw.

In an Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401 study, SD rats (5/sex/dose) were administered a single dose (1000, 1710, 2924 or 5000 mg/kg bw) of the chemical by oral gavage, and observed for 14 days. Signs of toxicity at the three highest doses included ptosis, decreased respiratory rate, pallor of extremities, loss of righting reflex and vocalisation. At necropsy, abnormalities were observed in the lungs (congested, red), liver (pale/dark/mottled) and stomach (ulceration, haemorrhage). The calculated LD50 was 2236 mg/kg bw for males and 2489 mg/kg bw for females (a combined LD50 of 2359 mg/kg bw) (EU RAR, 2008; REACH).

In another OECD TG 401 study, a single dose of 2000 mg/kg bw of TDCPP in corn oil was administered by oral gavage to SD rats (5/sex). Animals were observed for 14 days. There were 2 mortalities on day 4 (2 females). Clinical signs of toxicity included ataxia (lack of voluntary coordination of muscle movement), piloerection (bristling of hairs), hypokinesia (excessive muscular activity), soiled coat, chromodacryorrhoea (red lacrimal secretion), dacryorrhoea (excessive secretion of tears), rhinorrhoea (runny nose) and salivation. No abnormalities were observed at necropsy. A range-finding preliminary study was conducted prior to the main study. The SD rats (2/sex/dose) were administered 1000, 2000, 3000, 4000 or 5000 mg/kg bw of TDCPP. At dose levels 3000, 4000 and 5000 mg/kg bw, all animals died 1–2 days after dosing. In surviving animals, clinical signs included coma, piloerection, soiled coat, clonic convulsions, chromodacryorrhoea, dacryorrhoea, rhinorrhoea and excess salivation. No abnormalities were observed at necropsy. The oral LD50 was >2000 mg/kg bw (EU RAR, 2008; REACH).

In a non-guideline study, Dutch-Belted rabbits (5 males/dose) were administered a single dose (5000, 7500, or 10 000 mg/kg bw) of TDCPP (undiluted), by oral gavage and observed for 14 days following administration. Clinical signs included ataxia, prostration, teeth-grinding, shallow respiration, laboured respiration, diarrhoea, salivation, head nodding, and biting of cage bars. Findings in decedents at necropsy included congested lungs, red splotchy lungs, pale livers, white foci on the liver, purple spleens, yellow foci on the small intestine, and pale kidneys. Survivors appeared normal at necropsy. The calculated LD50 was 6800 mg/kg bw (EU RAR, 2008; REACH).

Dermal

The chemical has low acute toxicity following dermal exposure. The reported dermal LD50 in rats is >2000 mg/kg bw.

In an OECD TG 402 study, a single dose of 2000 mg/kg bw TDCPP was applied occlusively to the clipped skin of SD rats (5/sex/dose) for 24 hours. Observations were made for 14 days. There were no clinical signs of toxicity and no mortalities. No abnormalities were detected at necropsy. The dermal LD50 was >2000 mg/kg bw (EU RAR, 2008; REACH).

In a non-guideline study, 4640 mg/kg bw of TDCPP was applied on skin of 4 New Zealand White (NZW) rabbits (sex unspecified) using an occlusive dressing for 24 hours. There were no mortalities and no clinical signs of toxicity. The LD50 was >4640 mg/kg bw (REACH).

Inhalation

The chemical has low acute toxicity following inhalation exposure. The reported medial lethal concentration (LC50) in rats is >5.22 mg/L/4 hours.

In an OECD TG 403 study, SD rats were exposed to TDCPP as a liquid aerosol via nose only, for 4 hours at measured concentrations of 2.07 (2/sex), 1.16 (2/sex), 5.22 mg/L air (5/sex). Animals were observed for 14 days. There were no mortalities. No clinical signs of toxicity were observed and no abnormalities were detected at necropsy. The inhalation LC50 was >5.22 mg/L (EU RAR, 2008; REACH).

In a non-guideline study, SD rats (5/sex) were exposed to a nominal concentration of 9.8 mg/L for 1 hour in a 32 L positive presentation inhalation chamber, and observed for 14 days following exposure. There were no mortalities, and moderate depression was the only clinical sign of toxicity observed (REACH).

Corrosion / Irritation

Skin Irritation

Based on skin irritation studies in rabbits, the chemical may be slightly irritating to the skin.

In an OECD TG 404 study, 0.5 mL of TDCPP (neat) was applied semi-occlusively to the clipped and intact skin of 3 NZW rabbits (1 male, 2 female) for 4 hours, after which the skin was washed. Observations were made at 1, 24, 48 and 72 hours. Well-defined erythema (grade 2) was observed after 1 hour for 2/3 animals. This persisted to 24 hours in 1 of the 2 animals. Very slight erythema (grade 1) was recorded at 1 hour in the third animal. No oedema was observed. All reactions were reversed by 48 hours (EU RAR, 2008; REACH).

In a non-guideline study, 0.5 mL of TDCPP (neat) was applied occlusively to the intact abraded skin of NZW rabbits (6 animals, sex unspecified) for 24 hours. Animals were observed at 24 hours and 72 hours after patch removal. All 6 animals had slight to moderate erythema (grade 1–2), which was reversed by 72 hours. No oedema was observed (EU RAR, 2008; REACH).

Eye Irritation

Based on eye irritation studies in rabbits, the chemical may be slightly irritating to the eyes.

In an OECD TG 405 study, TDCPP (0.1 mL; neat) was instilled into the right eye of 3 NZW rabbits (2 male, 1 female) and the eyelids held closed for 1–2 seconds. The untreated left eye in each animal served as a control. Eyes were examined at 1, 24, 48 and 72 hours after instillation. Slight conjunctival erythema was observed in all animals after 1 hour. This was reversed by 24 hours. No other effects were reported (EU RAR, 2008; REACH).

In a non-guideline study, TDCPP (either as 0.1 mL of liquid or as 100 mg of solid; neat) was instilled into one eye each of 9 NZW rabbits (sex unspecified) and the eyelids held closed for 1 second. After 20–30 seconds, the substance was washed out with lukewarm water for 1 minute in the eye of 3/9 animals. The other 6 animals remained unwashed. Observations were made at 1, 2, 3, 4 and 7 days after instillation. No effects were reported (EU RAR, 2008; REACH).

Sensitisation

Skin Sensitisation

The chemical is not expected to be a skin sensitiser.

In an OECD Guideline 406 Guinea Pig maximisation test (GPMT), TDCPP showed no evidence of dermal sensitisation. Hartley guinea pigs (10/sex) were intradermally induced with 25 % TDCPP in corn oil. Animals were topically induced with 100 % TDCPP (preceded by a topical application of 10 % sodium lauryl sulphate). Ten control animals (5/sex) received the vehicle only. Dermal challenge with 100 % TDCPP did not result in signs of erythema or oedema in any of the test or control animals. A positive control study conducted using mercaptobenzothiazole gave appropriate responses (EU RAR, 2008; REACH).

Observation in humans

Male workers at TDCPP manufacturing plant (93 exposed and 31 non-exposed) were surveyed to determine whether occupational exposure to TDCPP caused adverse health effects (for more study details, see **Observation in Humans** in **Repeated Dose Toxicity** section). Slightly higher levels of dermatitis (6.5 %) were observed in the exposed group, compared to the non-exposed group (3.2 %) (US EPA, 2015).

Repeated Dose Toxicity

Oral

Based on the available information, the chemical has slight to moderate adverse effects on the health of mice and rats (mainly the liver and kidneys) from repeated oral exposure.

In a 90-day non-guideline study, slc/ddY mice (Ins2-Ccl21-leu (commonly referred to as SLC) transgenic mice crossed with Deutchland, Denken and Yoken (ddY) strain mice) (12/sex/dose) were fed diets containing TDCPP (0, 100, 400, 1300, 4200 or 13 300 ppm) for 3 months. The daily intake of TDCPP was 0, 13, 47, 171, 576 or 1792 mg/kg bw/day for males and 0, 15, 62, 214, 598 or 1973 mg/kg bw/day for females. In the 13 300 ppm group, both sexes displayed emaciation, rough hair and tremor, and all animals of this group died within 1 month. There were statistically significant increases in relative liver weights at 171 mg/kg bw/day and above in males and 47 mg/kg bw/day and above in females. There were also statistically significant increases in relative kidney weights in males at 576 mg/kg bw/day and above and in females at 171 mg/kg bw/day and above. Slight necrosis was observed in the livers of 2 females of the 576 mg/kg bw/day group. The NOAEL was 47 mg/kg bw/day in males and 15 mg/kg bw/day in females based on changes in liver weights (Kamata, 1989; WHO EHC, 1998; Environment and Climate Change Canada, 2016).

In a 24-month carcinogenicity study, SD rats (60/sex/dose) were fed diets containing TDCPP (approximately 0, 5, 20 or 80 mg/kg bw/day). An interim group (10/sex/dose) was sacrificed after 12 months of treatment. Mortality rates during the first 12 months were comparable between control and all treated groups. Mortality rates increased after month 17 in all groups and remained high until the end of the study. There was significantly greater mortality in high-dose males. There were decreases in body weight in high dose groups throughout the study, with body weights at termination of the study >20 % lower than controls. Absolute and relative weights of the kidney, liver and thyroid were significantly increased in high-dose groups for both sexes, at both 12 and 24 months. Significant increases in liver weight in the mid-dose group were also observed in some cases (absolute liver weights in males and relative liver weights in females). Relative heart weights were significantly increased in high-dose males and females at 12 and 24 months, and in the mid-dose males at 24 months. Non-neoplastic histological abnormalities in the liver (masses, nodules, raised areas, discolourations) were observed at higher incidence in TDCPP treated groups compared to controls at 24 months. Histological findings in the liver at 12 months were similar to controls. In the kidneys, enlargement, discolourations, surface irregularities, masses, nodules, and cysts were observed at 12 months. Chronic nephropathy was observed at 24 months. There were significant reductions in red blood cell parameters (decreases in the haemoglobin, haematocrit, and total erythrocyte counts) among high dose male and female rats (EU RAR, 2008; OECD SIAP, 2009; OEHHA, 2011; Environment and Climate Change Canada, 2016).

Dermal

No experimental data are available for the chemical.

Inhalation

No experimental data are available for the chemical.

Observation in humans

A total of 124 male full-time workers at a TDCPP manufacturing plant were surveyed to determine whether occupational exposure to TDCPP increased the incidence of respiratory conditions. Workers were employed for a minimum of 3 months between 1956 and 1977, and were classified as TDCPP-exposed (93 workers) or non-exposed (control; 31 workers). Sampling of the breathing zone was taken in the plant between December 1978 and May 1979, and the exposure concentration was calculated to be near the limit of detection of 8 ppb (140 µg/m^3). The survey consisted of a self-administered health questionnaire, physical examination, pulmonary function test, chest x-ray, electrocardiogram, and clinical and biochemical analyses. There were no abnormal clinical findings and no increased risk of adverse respiratory effects in workers exposed to TDCPP. An excess of benign neoplasms (primarily lipomas) (5.4 % versus 0 %), dermatitis (6.5 % versus 3.2 %) and gynaecomastia (3.3 % versus 0 %) was observed in the exposed group. However the study involved very few exposed workers and exposures were low (US EPA, 2015; OECD SIAP, 2009; WHO EHC, 1998).

Genotoxicity

A number of studies were available on the mutagenic potential of TDCPP in vitro and in vivo. Overall, TDCPP gave some positive results in vitro, but all results were negative in vivo.

In vitro studies

The chemical was positive in the following in vitro genotoxicity studies (OECD SIAP, 2009; REACH):

- a bacterial reverse mutation assay in *Salmonella typhimurium* strains TA 1535, TA 1537, TA 92, TA 98 and TA 100 exposed to 500 µg /mL of the chemical with metabolic activation only;
- a bacterial reverse mutation assay in *S. typhimurium* strain TA 100 treated with the chemical (50, 100, 250, 500, and 1000 µg/plate), with and without metabolic activation with S9 mix. The chemical was mutagenic with metabolic activation in a dose-response fashion (maximal response at 500 µg/plate) and cytotoxic at 1000 µg/plate;
- a mammalian chromosome aberration test in mouse lymphoma L5179Y cells at concentration of 40 µg/mL, with metabolic activation only;
- a mammalian chromosome aberration test in mouse lymphoma L5178Y cells treated with 0.002–0.098 µL/mL of the chemical. There was a dose-related trend (non-significant) in the induction of chromosome aberrations at 0.004–0.072 µL/mL, with metabolic activation; and
- a mammalian chromosome aberration test in Chinese hamster lung fibroblasts (V79) exposed to 500 µg /mL of the chemical, with and without S9 activation. TDCPP induced chromosomal aberrations with metabolic activation.

The chemical was negative in the following in vitro genotoxicity studies (OECD SIAP, 2009; REACH):

- a bacterial reverse mutation assay (GLP compliant) conducted according to Safepharm Standard Test Method M26 in *S. typhimurium* strains TA 1535, TA 1538, TA 1537, TA 98 and TA 100 exposed up to 125 000 µg/mL of the chemical, in the presence and absence of S9 mix;
- an OECD TG 473 mammalian chromosome aberration test with Chinese hamster ovary (CHO) cells exposed up to 100 or 10 µg/mL of the chemical with and without metabolic activation with S9 mix, respectively;
- a sister chromatid assay in mouse lymphoma L5178Y cells treated with the chemical at concentrations of 0.002–0.098 µL/mL; and
- a mammalian cell transformation assay in BALB/3T3 cells (mouse embryonic fibroblast cell line) treated with 0.12–0.312 µL/mL of the chemical.

In vivo studies

The chemical did not induce unscheduled DNA synthesis (OECD TG 486) in hepatocytes of the male and female Harlan SD (Hsd:SD) rats administered 500, 1000 or 2000 mg/kg bw TDCPP by oral gavage and evaluated at 2–4 hours or 14–16 hours after administration (4 or 6 animals/time point, sex unspecified) (OECD SIAP, 2009; REACH).

The chemical was negative in an erythrocyte micronucleus test (OECD TG 747) using CFLP mice (5/sex/dose) administered a single dose of TDCPP (0, 200, 630 or 2000 mg/kg) by oral gavage.

The chemical was not clastogenic in a mouse bone marrow chromosome aberration assay. Male CD-1 mice were fed TDCPP (0.5 mL/kg, 0.17 mL/kg, 0.05 mL/kg). In the acute test, 8 mice per time point of sacrifice were dosed with TDCPP and sacrificed at 6, 24, or 48 hours post-dosing. In the subchronic test, 8 mice were dosed each day for 5 days and sacrificed 6 hours after the final dose (OECD SIAP, 2009; REACH).

Carcinogenicity

The chemical is classified as hazardous—Category 2 carcinogenic substance—with the risk phrase ‘Suspected of causing cancer” (H351) in the HCIS (Safe Work Australia). The data from an oral carcinogenicity study in rats support this classification.

In a 24-month oral carcinogenicity non-guideline study, SD rats (60/sex/dose) were fed diets containing TDCPP up to doses of 80 mg/kg bw/day (see **Repeated Dose Toxicity** section). At the 12 month interim sacrifice, no significant increases of any tumour types compared to controls were observed in any of the treatment groups. At 24 months, exposure to TDCPP caused statistically significant increases in tumours at multiple sites. The high-dose male rats showed significant increases in incidence of liver tumours (hepatocellular adenoma, hepatocellular carcinoma, and combined hepatocellular adenoma/carcinoma) while mid- (20 mg/kg bw/day) and high-dose (80 mg/kg bw/day) males showed significant increases in incidence of kidney (renal

cortical adenoma) and testicular (interstitial cell tumour) tumours. Among high-dose females, statistically significant increases in hepatocellular adenomas, and combined hepatocellular adenomas/carcinomas were observed (EU RAR, 2008; OECD SIAP, 2009; OEHHA, 2011; Environment and Climate Change Canada, 2016; REACH).

Hyperplasia, which may be pre-neoplastic, was observed at the low dose in the same organs as tumours were observed. There were an increased incidence of parathyroid hyperplasia in high-dose animals; erythroid/myeloid hyperplasia of the rib marrow; and erythroid/myeloid metaplasia of the spleen. A LOAEL of 5 mg/kg bw/day was derived based on an increase in the incidence of hyperplasia in the kidneys in males (EU RAR, 2008; OECD SIAP, 2009; OEHHA, 2011; Environment and Health Canada, 2016; REACH).

Observation in humans

In a retrospective cohort study, the mortality of workers employed at a TDCPP manufacturing plant was investigated. Male workers (289 workers, age unspecified) who were employed for a minimum of 3 months during the 1957–77 study period were followed through to 1980. Fifty percent of the workers had worked at the plant for less than 5 years while 42 workers had worked for 15 years or more. The vital status (living or deceased) was evaluated as of December 31, 1980. Ten workers died during the study period. All workers were exposed to very low levels of TDCPP in the work environment (below the detection limit of 8 ppb). The overall mortality was 75 % of that expected in a comparable population of males in the US. Mortality due to malignant neoplasms was slightly higher than expected, with a standardised mortality ratio (SMR = observed deaths/expected deaths x 100) of 131. Three cases of lung cancer were observed, compared to 0.8 expected. However, all 3 workers were moderate to heavy cigarette smokers, which may have confounded the diagnosed lung cancers. Overall, it was concluded there was no evidence linking TDCPP exposure with lung cancers. Since liver, kidney and testicular tumours were found in the 24-month carcinogenicity study in rats (see the above study in **Carcinogenicity** section), this study also aimed to determine whether tumours would occur in humans at these sites. No liver, kidney, and testicular cancers were observed. However, as this was a small study, the study findings may not be highly reliable (EU RAR, 2008; OECD SIAP, 2009; OEHHA, 2011; Environment and Health Canada, 2016; REACH).

Reproductive and Developmental Toxicity

The chemical was not toxic to reproduction in rabbits and developmental toxicity was reported only at maternally toxic doses in rats.

In a non-guideline study, pregnant female Wistar rats (15–24 per group) were administered TDCPP (in olive oil) by oral gavage, at doses of 0, 25, 50, 100, 200 or 400 mg/kg bw/day, on days 7 to 15 of gestation. There was severe maternal toxicity in the 400 mg/kg group, with a marked suppression in maternal body weight gain (17 % decrease) and food consumption, and death in 11 out of 15 dams. Clinical effects at 400 mg/kg included piloerection, salivation and haematuria. Absolute and relative kidney weights were significantly increased in dams in the 200 mg/kg group. No effects on dams were observed at lower doses. Foetal lethality was increased at 400 mg/kg (26 compared to 6 in the control group). At 200 mg/kg or less, there was no evidence of increased foetal deaths, abnormal foetal development, or malformation. At 200 mg/kg bw/day and below, performance of pups from treated dams in functional tests (open field, water maze, rotarod, inclined screen, pain reflex and Preyer’s reflex) were comparable to results from the control group. The NOAEL for maternal toxicity was 100 mg/kg bw/day based on a significant increase in absolute and relative kidney weights at the next dose level (200 mg/kg bw/day). The developmental NOAEL was 200 mg/kg bw/day, based on a significant increase in foetal deaths at the next dose level (400 mg/kg bw/day) (WHO EHC, 1998; OECD SIAP, 2009; Environment and Climate Change Canada, 2016; REACH).

In a non-guideline fertility study, male Dutch rabbits were administered 2, 20 or 200 mg/kg bw/day of TDCPP by oral gavage for 12 weeks prior to mating. Treatment did not affect mating, fertility, pregnancy parameters, sperm quantity or sperm quality. No histopathological changes were observed in the male reproductive tract. No effects were seen in pituitaries, testes or epididymis (WHO EHC, 1998; OECD SIAP, 2009; Environment and Climate Change Canada, 2016).

In a 24-month non-guideline study, SD rats (60/sex/dose) were fed diets containing up to 80 mg/kg bw/day TDCPP (see **Repeated Dose Toxicity** section). Abnormalities were detected at 24 months in the mid- (20 mg/kg bw/day) and high-dose (80 mg/kg bw/day) groups in the testes (enlargement, nodules, masses, flaccidity, discolourations). Abnormalities in the seminal vesicles (atrophy, decreased secretory product) were seen at 24 months in all treated groups. A LOAEL of 5 mg/kg bw/day was based on the abnormalities observed in the testes (EU RAR, 2008; OECD SIAP, 2009; Environment and Climate Change Canada, 2016; REACH).

Other Health Effects

Neurotoxicity

Neurotoxicity is a potential adverse effect of many organophosphates, but the potency levels that may cause neurotoxicity varies significantly. Based on the limited available information, the chemical may be weakly neurotoxic but does not induce typical organophosphate delayed neurotoxicity.

In a 90-day non-guideline neurotoxicity study, white Leghorn hens (10/dose) were administered up to 100 mg/kg bw/day of TDCPP (in corn oil) by oral gavage daily for 90 days. Positive controls were treated with tri-o-cresyl phosphate (TOCP) and vehicle controls were treated with corn oil. There was no evidence of delayed neurotoxicity in control or TDCPP treated hens. All hens treated with the positive control showed evidence of delayed neurotoxicity (EU RAR, 2008; OECD SIAP, 2009; US EPA, 2015; REACH).

In a 24-month carcinogenicity study in SD rats (60/sex/dose) fed diets containing up to 80 mg/kg bw/day TDCPP (see **Repeated Dose Toxicity** and **Carcinogenicity** sections), plasma cholinesterase activity and erythrocyte cholinesterase activity were measured at 18 and 24 months. There was a significant decrease in plasma cholinesterase activity in high-dose females at 18 months, and a non-significant decrease at 24 months. There was no dose-response trend in plasma cholinesterase activity in males at 18 months. Levels in males were comparable to controls at 24 months. Erythrocyte cholinesterase activity at 18 and 24 months was comparable between treated and control groups for both sexes (US EPA, 2015).

In an in vitro study, the neurotoxicity potential of TDCPP was evaluated at concentrations of 10, 20, and 50 µM in undifferentiated and differentiated PC12 cells, with positive control being the organophosphate pesticide chlorpyrifos (CPF), a known developmental neurotoxicant. TDCPP caused concentration-dependent inhibition of DNA synthesis, decrease in cell number and altered neurodifferentiation, with effects that were equivalent or greater than equimolar concentrations of CPF. TDCPP caused elevated oxidative stress (22 % increase in lipid peroxidation) at the high concentration, but had no adverse effect on cell viability or growth (Dishaw et al., 2011).

In a long-term study investigating the effects of TDCPP on the zebrafish nervous system, zebrafish embryos (2 hours post fertilisation) were exposed to 0, 4, 20 and 100 µg/L of TDCPP for 6 months until sexually mature. Locomotor activity, acetylcholinesterase activity (a biomarker for the presence of neurotoxicants), levels of neurotransmitters (dopamine and serotonin) and expression of mRNAs and proteins related to nervous system development were not affected in any dose group. However, in adult fish, there were reductions in dopamine and serotonin levels in the brains of female fish. Levels of these neurotransmitters were not affected in adult males. In the brain tissue of both sexes, there was downregulation of genes involved in nervous system development (Wang et al., 2015c; Environment and Climate Change Canada, 2016).

In a chronic study, neuronal development was studied in the F1 progeny of adult zebrafish exposed to 0–100 µg/L of TDCPP for 3 months (see **Toxicokinetics** section). The mRNA and protein expression of factors associated with neuronal development were significantly downregulated in F1 progeny of exposed adults, as was the level of the neurotransmitters dopamine, serotonin, gamma amino butyric acid, and histamine. The result was a significant decrease in larval locomotion, but no effect on acetylcholinesterase activity (Wang et al., 2015a; Environment and Climate Change Canada, 2016).

Endocrine Disruption

Recent in vitro and non-mammalian studies suggest that the chemical can cause perturbations to the endocrine system, by altering steroid hormone levels or binding the steroid hormone receptors. These perturbations in endocrine system suggest potential endocrine activity, indicative of a possible mechanism for causation of adverse effects. The likelihood that these would lead to any adverse effects downsteam is currently unknown. Further information is required to evaluate the hazard potential and risk to human health.

The endocrine activity of TDCPP was investigated in a human adrenocortical cell line (H295R cells) and a breast carcinoma cell line derived from human breast adenocarcinoma cells (MVLN cells). H295R cells were used to measure sex hormone synthesis and steroidogenic gene expression. Treatment of H295R cells with the chemical significantly increased production of testosterone and oestradiol, leading to significantly elevated concentrations in the cell media. Gene expressions of steroidogenic

enzymes were also up-regulated. MVLN cells were used to evaluate oestrogen receptor binding activity of the chemical. The chemical inhibited oestrogen receptor binding by acting as a receptor antagonist (Liu et al., 2012; US EPA, 2015; HSDB).

In an in vitro study, the potential agonistic and antagonistic activities of TDCPP against human nuclear receptors were examined in Chinese hamster ovary cells using cell-based transactivation assays (CHO-K1). The chemical was found to act as a receptor agonist at pregnane X receptor (PXR), and a receptor antagonist at androgen receptor (AR) and glucocorticoid receptor (GR). The activities were 5-, 100- and 300-fold lower than known PXR agonist (rifampicin), AR antagonist (hydroxyflutamide) and GR antagonist (mifepristone), respectively (Environment and Health Canada, 2016).

Multiple non-guideline studies in zebrafish has shown that TDCPP may alter steroid pathways including androgen, estrogen and thyroid hormones and influence embryo hatching and survival (Liu et al., 2012; Liu et al., 2013a; Liu et al., 2013b; Wang et al., 2013; Wang et al., 2015a; Wang et al., 2015b). While suggesting endocrine activity for the chemical, the relevance of these non-guideline findings on adverse effects in humans requires further investigation.

A recent epidemiological study examined possible effects of the endocrine activity potential of the chemical seen in in vitro assays and non-mammalian studies. In a cross-sectional study, blood and house dust samples were collected from 50 male participants (aged 18–54 years) recruited through a U.S. infertility clinic, and analysed for the chemical. An interquartile range (IQR) increase in TDCPP in dust was associated with 3 % decline in free T4 and a 17 % increase in prolactin levels in blood (Meeker and Stapleton, 2010; US EPA, 2015; Environment and Health Canada, 2016; HSDB).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include the systemic long-term effect of carcinogenicity.

Public Risk Characterisation

Given the use of the chemical in domestic and commercial products, the public could be exposed to the chemical through oral, dermal and inhalation routes. The public may be directly exposed via articles or coated surfaces containing the chemical. While flame retardants are retained well in intact articles containing e.g. polyurethane foam (EU RAR, 2008), there is potential for them to be released if the article breaks down into smaller pieces or dust. The chemical could be released from articles through abrasion or dissolution (ATSDR, 2012).

Of particular importance is the exposure of babies and young children to the chemical due to their higher contact with floors, frequent hand-to-mouth contact, and mouthing of objects. Since infants are at very critical stages of development, intimate contact with a potentially hazardous material is of even greater concern. The chemical TDCPP has been detected in baby products overseas (Stapleton et al., 2011). However, the use of the chemical in such products in Australia is unknown. The chemical is also commonly detected in house dust (Stapleton et al., 2009; Takigami et al., 2009; Meeker and Stapleton, 2010; Meeker et al., 2013; Harrad et al., 2016). However, the exposure to the chemical is expected to be low. The estimated margins of exposure (MOE) for the chemical through dermal exposure in infants or mouthing of foam objects in toddlers were >2600 and >25000, respectively (Environment and Climate Change Canada, 2016; EU RAR, 2008).

Therefore, the public risk is not expected to be unreasonable.

Occupational Risk Characterisation

During product formulation of the chemical, oral, dermal and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effect of carcinogenicity, the chemical could pose an unreasonable risk to workers unless adequate control measures to minimise 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 for carcinogenicity support the hazard classification in the HCIS (Safe Work Australia). The data for reproductive and developmental toxicity and endocrine effects are not conclusive, and further information is required to assess these potential adverse effects in humans.

NICNAS Recommendation

Current risk management measures are considered adequate to protect public and workers' health and safety, provided that all requirements are met under workplace health and safety as adopted by the relevant state or territory.

There are indications of effects associated with hormone concentration changes in animals treated with the chemical. However, the available data do not demonstrate the potential of the chemical to cause adverse effects via endocrine activity. NICNAS will continue to monitor the availability of high quality data emerging on the chemical and determine if further assessment may be required.

Regulatory Control

Work Health and Safety

The chemical is 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]
Carcinogenicity	Not Applicable	Suspected of causing cancer - Cat. 2 (H351)*

[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 chemical 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 chemical should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the

physical form and the manner in which the chemical is used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

References

Agency for Toxic Substances and Disease Registry (ATSDR) (2012). Toxicological Profile For Phosphate Ester Flame Retardants. Accessed November 2017 at https://www.atsdr.cdc.gov/toxprofiles/tp202.pdf

California Environmental Protection Agency (California EPA) (2013). Chemicals known to the state to cause cancer or reproductive toxicity October 27, 2017. Accessed November 2017 at https://oehha.ca.gov/media/downloads/proposition-65//p65102717.pdf

Carignan CC, McClean MD, Cooper EM, Watkins DJ, Fraser AJ, Heiger-Bernays W, Stapleton H, Webster TF (2013). Predictors of tris(1,3-dichloro-2-propyl) phosphate metabolite in the urine of office workers. Environ Int 55: 56–61.

Commonwealth of Massachusetts Bill S.2293 (2016). An Act to protect children and families from harmful flame retardants. Accessed November 2017 at https://malegislature.gov/Bills/189/S2293/Amendments/Senate

Dishaw LV, Hunter DL, Padnos B, Padilla S, Stapleton HM (2014). Developmental exposure to organophosphate flame retardants elicits overt toxicity and alters behaviour in early life stage zebrafish (Danio rerio). Toxicol Sci 142: 445–454

Dishaw LV, Powers CM, Roberts SC, Seidler FJ, Slotkin TA, Stapleton HM (2011). Is the PentaBDE replacement, tris (1,3-dichloro-2-propyl) phosphate (TDCPP), a developmental neurotoxicant? Studies in PC12 cells. Toxicol Appl Pharmacol 256: 281–289

District of Columbia (2016). Carcinogenic Flame Retardant Prohibition Amendment Act of 2016 (B21-143). Accessed November 2017 at http://lims.dccouncil.us/Download/33567/B21-0143-SignedAct.pdf

Environment and Climate Change Canada (2016). Draft Screening Assessment. Certain Organic Flame Retardants Substance Grouping. Accessed October 2017 at http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=B4374491-1

European Union Risk Assessment Report (EU RAR) (2008). Tris [2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP). Accessed October 2017 at https://echa.europa.eu/documents/10162/13630/trd_rar_ireland_tdcp_en.pdf

Galleria Chemica. Accessed October 2017 at https://jr.chemwatch.net/galleria/

Harrad S, Brommer S, Mueller JF (2016). Concentrations of organophosphate flame retardants in dust from cars, homes, and offices: An international comparison. Emerging Contaminants 2: 66–72

Kamata E, Naito K, Nakaji Y, Ogawa Y, Suzuki S, Kaneko T, Takada K, Kurokawa Y, Tobe M (1989). Acute and subacute toxicity studies of tris(1,3-dichloro-2-propyl) phosphateon mice. Bull Natl Inst Hyg Sci 107: 36–43

Kim JW, Isobe T, Muto M, Tue NM, Katsura K, Malarvannan G, Sudaryanto A, Chang K-H, Prudente M, Viet PH, Takahashi S, Tanabe S (2014). Organophosphorus flame retardants (PFRs) in human breast milk from several Asian countries. Chemosphere 116: 91–97

Liu C, Wang Q, Liang K, Liu J, Zhou B, Zhang X, Liu H, Giesy JP, Yu H (2013b). Effects of tris(1,3-dichloro-2-propyl) phosphate and triphenyl phosphate on receptor-associated mRNA expression in zebrafish embryos/larvae. Aquatic Toxicology 128-129:147–157

Liu X, Ji K, Choi K (2012). Endocrine disruption potentials of organophosphate flame retardants and related mechanisms in H295R and MVLN cell lines and in zebrafish. Aquat Toxicol 114–115: 173–181

Liu X, Ji K, Jo A, Moon HB, Choi K (2013a). Effects of TDCPP or TPP on gene transcriptions and hormones of HPG axis, and their consequences on reproduction in adult zebrafish (Danio rerio). Aquat Toxicol 134–135: 104–111

Meeker JD, Cooper EM, Stapleton HM, Hauser R (2013). Urinary metabolites of organophosphate flame retardants: temporal variability and correlations with house dust concentrations. Environ Health Persp 121: 580–585

Meeker JD, Stapleton HM (2010). House dust concentrations of organophosphate flame retardants in relation to hormone levels and semen quality parameters. Environ Health Perspect 118: 318–323

Minegishi K, Kurebayashi H, Nambaru S, Morimoto K, Takahashi T (1987). Comparative studies on absorption, distribution, and exretion of flame retardants halogenated alkyl phosphate in rats. Eisei Kagaku 34: 102-114

NICNAS (2001). Triphosphates Priority Existing Chemical Assessment Report No. 17

Nomeir AA, Kato S, Matthews HB (1981). The metabolism and disposition of tris(1,3-dichloro-2-propyl) phosphate (Fyrol FR-2) in the rat. Toxicol Appl Pharmacol 57: 401-413

Organisation for Economic Co-operation and Development Screening information data set Initial Assessment Profile (OECD SIAP) (2009). Tris[2-chloro-1-(chloromethyl)ethyl] phosphate (TDCP). Accessed October 2017 at https://hpvchemicals.oecd.org/UI/handler.axd?id=d7a3df92-ea41-4378-bda4-51c09727ccbd

Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Dossier. Tris[2-chloro-1-(chloromethyl)ethyl] phosphate. Accessed November 2017 at https://echa.europa.eu/registration-dossier/-/registered-dossier/14365

Safe Work Australia Hazardous Chemicals Information System. Accessed November 2017 at http://hcis.safeworkaustralia.gov.au/ExposureStandards/Details?exposureStandardID=645

Stapleton HM, Klosterhaus S, Eagle S, Fuh J, Meeker JD, Blum A, Webster TF (2009). Detection of organophosphate flame retardants in furniture foam and U.S. house dust. Environ Sci Technol 43: 7490–7495

Stapleton HM, Klosterhaus S, Keller A, Ferguson PL, van Bergen S, Cooper E, Webster TF, Blum A (2011). Identification of flame retardants in polyurethane foam collected from baby products. Environ Sci Technol 45: 5323–5331

State of Washington (2016). Engrossed Substitute House Bill 2545, 64th Legislature, 2016 Regular Session. An Act relating to reducing public health threats that particularly impact highly exposed populations, including children and firefighters, but establishing a process for the department of health to restrict the use of toxic flame retardant chemicals in certain types of consumer products. Accessed November 2017 http://lawfilesext.leg.wa.gov/biennium/2015-16/Pdf/Bills/House%20Passed%20Legislature/2545-S.PL.pdf

Substances in Preparations in Nordic Countries (SPIN) Database. Accessed October 2017 at http://www.spin2000.net/spinmyphp/

Sundkvist AM, Olofsson U, Haglund P (2010). Organophosphorus flameretardants and plasticizers in marine and fresh water biota and in human milk. J Environ Monit 12: 943–951

Takigami H, Suzuki G, Hirai Y, Ishikawa Y, Sunami M, Sakai S (2009). Flame retardants in indoor dust and air of a hotel in Japan. Environ Int 35: 688-93

The European Commission (2014). Commission directive 2014/79/EU of 20 June 2014, amending Appendix C of Annex II to Directive 2009/48/EC of the European Parliament and of the Council on the safety of toys, as regards TCEP, TCPP and TDCP. Accessed November 2017 at http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014L0079&from=EN

The Office of Environmental Health Hazard Assessment's (OEHHA) Reproductive and Cancer Hazard Assessment Branch (2011). Evidence on the carcinogenicity of tris(1,3-dichloro-2-propyl) phosphate. Accessed November 2017 at https://oehha.ca.gov/media/downloads/proposition-65/chemicals/tdcpp070811.pdf

United States Consumer Product Safety Commission (US CPSC) (2017). Volume 82, No. 187. Notices. Accessed November 2017 at https://www.gpo.gov/fdsys/pkg/FR-2017-09-28/pdf/2017-20733.pdf

United States Environmental Protection Agency (US EPA) (2015). Flame Retardants Used In Flexible Polyurethane Foam: An Alternatives Assessment Update. Accessed October 2017 at https://www.epa.gov/sites/production/files/2015-08/documents/ffr_final.pdf

US EPA Toxic Substances Control Act (TSCA) (2015) Work Plan Chemical Problem Formulation and Initial Assessment. Chlorinated Phosphate Ester Cluster Flame Retardants. Accessed November 2017 at https://www.epa.gov/sites/production/files/2015-09/documents/cpe_fr_cluster_problem_formulation.pdf

US National Library of Medicine's Hazardous Substances Database (HSDB). National Library of Medicine. Testing Status of tris(1,3-Dichloro-2-propyl) phosphate 10923-J. Accessed October 2017 at https://ntp.niehs.nih.gov/testing/status/agents/ts-10923-j.html

US National Toxicology Program (NTP). Testing Status of (1,3-Dichloro-2-propyl) phosphate 10923-J. Accessed November 2017 at https://ntp.niehs.nih.gov/testing/status/agents/ts-10923-j.html

Wang Q, Lai NL-S, Wang X, Guo Y, Lam PK-S, Lam JW-H, Zhou B (2015a). Bioconcentration and transfer of the organophorous flame retardant 1,3-dichloro-2-propyl phosphate causes thyroid endocrine disruption and developmental neurotoxicity in zebrafish larvae. Environ Sci Technol 49: 5123–5132

Wang Q, Lam JCW, Han J, Wang X, Guo Y, Lam PKS, Zhou B (2015b). Developmental exposure to the organophosphorus flame retardant tris(1,3-dichloro-2-propyl) phosphate: Estrogenic activity, endocrine disruption and reproductive effects on zebrafish. Aquat toxicol 160: 163–171

Wang Q, Lam JW-H, Man Y-C, Lai NL-S, Kwok KY, Guo Y, Lam PK-S, Zhou B. (2015c). Bioconcentration, metabolism and neurotoxicity of theorganophorous flame retardant 1,3-dichloro 2-propyl phosphate(TDCPP) to zebrafish. Aquatic Toxicology 158: 108-115

Wang Q, Liang K, Liu J, Yang L, Guo Y, Liu C, Zhou B (2013). Exposure of zebrafish embryos/larvae to TDCPP alters concentrations of thyroid hormones and transcriptions of genes involved in the hypothalamic–pituitary–thyroid axis. Aquat

Toxicol 126: 207–213

World Health Organisation (WHO EHC) Environmental Health Criteria 209 (1998). Accessed November 2017 at http://www.who.int/ipcs/publications/ehc/who_ehc_209.pdf

Last update 02 March 2018

Share this page