Xylyl phosphate esters: Human health tier II assessment

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Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phenol, dimethyl-, phosphate (3:1)	25155-23-1
Phosphoric acid, dimethylphenyl diphenyl ester	29660-68-2
Tar acids, cresylic, C8 rich, phosphates	68952-33-0

Preface

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

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

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

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

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to

human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

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

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

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

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

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The substances in this group are produced through the reaction of phosphorus oxytrichloride and xylenols. The xylenols (dimethylphenols) are either produced synthetically or are derived from coal tar or petroleum refining (tar acids). The xylenols contain other high-boiling phenolic fractions like ethyl phenols and propyl phenols. All substances are Unknown or Variable Composition, Complex Reaction Products and Biological Materials (UVCB) substances containing various different constituents. The substances generally contain a large number of possible isomers that cannot be easily analysed.

The substances differ in the number of phenyl rings that are substituted. The substance trixylyl phosphate (TXP; CAS No. 25155-23-1) predominantly has all phenyl rings dimethylated (xylyl groups), while the chemical diphenyl xylyl phosphate (CAS No. 29660-68-2) has one methylated xylyl group and two unmethylated phenyl rings. These substances are mixtures of isomers varying in the position of methylation in the xylyl rings both relative to each other and relative to the phosphate with ortho (o), para (p) or meta (m) methylation.

Two commercial TXP products, contained the following xylenol isomers in decreasing order of abundance: 2,5-, 2,3-, 3,5-, 2,4- and 3,4- isomers. The 2,6-isomer was not present. The phosphate esters of the individual isomers are not listed on the AICS. Other components identified included 4-ethylphenol, p-cresol, phenol and trimethyl phenol (EHCA, 2013).

Tar acids, cresylic, C8-rich, phosphates (CAS No 68952-33-0) refer to the phosphate esters converted from a C8-rich distillation fraction derived from coal tar derived tar acids. The C8-rich distillation fraction is expected to mainly contain the c8-fraction including xylenols with and ethyl phenols with varying substitution patterns.

The substances have similar uses as plasticisers and flame retardants.

The substances may also present in a commercial flame retardant mixtures including tricresyl phosphate (TCP; CAS No. 1330-78-5). Information is available for other substituted aryl phosphate ester flame retardants (NICNASa; NICNASb), and the chemicals are expected to have similar toxicity profiles.

Import, Manufacture and Use

Australian

The following uses were identified for the substance TXP based on publicly available safety data sheets (SDS) for products containing the chemical sold in Australia.

The substance TXP may have commercial use as additive in compressor oils and epoxy adhesives and site-limited uses in fire resistant hydraulic fluids.

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

International

The following international uses have been identified for the substance TXP (CAS No 25155-23-1) through Galleria Chemica, the United States (US) National Library of Medicine's Hazardous Substances Data Bank (HSDB), The European Chemicals Agency (ECHA, 2013); the European Union (EU) Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) dossier; United States Environmental Protection Agency (US EPA) Chemical and Product Categories (CPCat) database; and the Substances and Preparations in Nordic countries (SPIN) database.

The substance TXP has possible commercial uses including

- as functional fluids (fire resistant fluids, hydraulic fluids, lubricants, lubricant additives, grease products);
- in jet engine oils; and
- in surface coatings.

The substance TXP may have site-limited uses, including in manufacture of flame retarded fluids, plastics and textiles, including polyurethane foams, high performance hydraulic fluids, lubricants, metal working fluids and resins.

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

Based on publicly available SDS for the products containing Tar acids, cresylic, C8-rich, phosphates (CAS No. 68952-33-0) sold internationally, the substance has commercial use as a flame retardant. The substance was listed on the Substances and Preparations in Nordic countries (SPIN) database with confidential use information only.

No specific uses were identified for the substance diphenyl xylyl phosphate (CAS No. 29660-68-2). Therefore, it is not expected to have significant uses as a pure substance, but rather present in various UVCB flame retardant mixtures as impurity (US EPA, 2015).

The substances are not expected to have domestic uses. The substance TXP is not used in the formulation of products intended for consumer use (ECHA, 2013) and the available North American databases do not give evidence for use of these substances in consumer products. However, a number of articles formulated to contain the substances as plasticisers or flame retardants are used in domestic settings and release of the chemical in dust can lead to public exposure.

Restrictions

Australian

No known restrictions have been identified.

International

The substance TXP (CAS No. 25155-23-1) is listed on the candidate list of substances of very high concern (SVHC) and has been prioritised for inclusion in Annex XIV in the European Union (EU) with no proposed exempted uses (ECHA, 2013; ECHA 2016).

In Maine, United States of America (USA) – Legislature is being implemented to restrict a flame retardant chemical or mixture that includes flame retardant chemicals to 0.1 % in new residential upholstered furniture containing fabrics, other coverings or cushioning materials. The restriction takes effect in 2019 (Maine Legislature, 2017).

Existing Worker Health and Safety Controls

Hazard Classification

The substance TXP (CAS No. 25155-23-1) is classified as hazardous, with the following hazard category and hazard statement for human health in the Hazardous Chemical Information System (HCIS) (Safe Work Australia).

Reproductive toxicity – category 1B; H360F (May damage fertility)

The other substances are not listed on the HCIS (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available.

International

An Occupational Exposure Limit (OEL) of 0.1 mg/m^3 exists for TXP (CAS No. 25155-23-1) in Canada (Ontario) (Galleria Chemica; ECHA, 2013).

Health Hazard Information

The substances in this group are xylyl phosphate esters differing in the number of phenol moieties that are substituted. The substances are mixtures of isomers varying in the position of methylation in the xylyl rings with ortho (o), para (p) or meta (m) methylation relative to the phosphate. The substances may also contain ethylphenol phosphate isomers (see ***Grouping Rationale*** section).

The majority of data available are for commercial TXP formulations, with some information for specific xylyl and ethylphenol isomers. Data for other aryl phosphate esters have been used to support limited data or in the absence of specific information for the substances in this assessment.

Toxicokinetics

No toxicokinetic data are available for the substances in this assessment.

Triaryl phosphate esters are generally readily absorbed via oral and dermal routes and excreted in urine (Sjogren et al., 2010).

Triaryl phosphate esters may be metabolised via various pathways but generally most lose one of the ester moieties to form phosphate diesters.

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

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

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

Acute Toxicity

Oral

Based on the available data for the substance TXP and certain ethyl phenyl phosphate esters, the substances are expected to have low acute toxicity following oral exposure. Following oral exposure, the median lethal dose (LD50) values for tri-o-ethylphenyl phosphate (CAS No 3862-08-6 not listed on the AICS), tri-m-ethylphenyl phosphate (CAS No 52736-14-8 not listed on the AICS) and TXP in rats are greater than 5000 mg/kg bw (Johannsen et al., 1977).

In an acute oral toxicity study consistent with the US EPA OTS 798.1175 guideline for registering pesticides, the acute oral LD50 for Fyrquel EHC (TXP; purity not specified) in male and female Sprague Dawley (SD) rats was >5000 mg/kg bw. A single oral dose of 5000 mg/kg bw of Fyrquel EHC produced no mortalities. Adverse clinical signs for all rats included mild to moderate depression, piloerection, and evidence of excessive urination. All rats appeared normal by day 7 (REACH).

Dermal

Based on the available data for the substance TXP and certain ethyl phenyl phosphate esters, the substances are expected to have low acute toxicity following dermal exposure. Following dermal exposure, the LD50 values for tri-o-ethylphenyl phosphate, tri-m-ethylphenyl phosphate and TXP in rabbits are greater than 2000 mg/kg bw (Johannsen et al., 1977).

In an acute dermal toxicity study consistent with the US EPA guidelines for registering pesticides in the USA, the acute dermal LD50 for Fyrquel EHC (TXP; purity not specified) in albino rabbits (strain not specified) was >2000 mg/kg bw. Mild erythema and oedema were reported following a 24 hour exposure. All rabbits appeared normal at necropsy (REACH).

Inhalation

No data are available. In general, triaryl phosphate esters have low acute toxicity by the inhalation route of exposure (Weiner and Jortner, 1999). Data available for TCP and other aryl phosphate esters support the absence of toxicity (NICNASa; NICNASb).

Corrosion / Irritation

Skin Irritation

Based on the available data for the substance TXP and other aryl phosphate esters, the substances are considered to be, at most, slight skin irritants.

In a skin irritation study consistent with older US EPA OTS 798.4470 guideline for registering pesticides, 6 Stauffland albino rabbits were dermally exposed to 0.5 mL of the Fyrquel EHC (TXP; purity not specified) under occlusive conditions for 4 hours. Mild erythema was reported in all rabbits at 24 hours but was reversible in four rabbits within 72 hours. Oedema was not detected in any rabbit at any time point (REACH).

In general, triaryl phosphate esters are non-irritating to skin (Sjogren et al., 2010). TCP and other substituted aryl phosphates are at most slight irritants in studies in rabbits (NICNASa; NICNASb).

Eye Irritation

Based on the available data for the substance TXP and other aryl phosphate esters, the substances are considered to be, at most, slight eye irritants.

In an eye irritation study consistent with US EPA OTS 798.4500 guideline for registering pesticides, 9 Stauffland albino rabbits received 0.1 mL of Fyrquel EHC (trixylenyl phosphate; purity not specified) into the right eye. The treated eye was washed with water 20-30 seconds after exposure in 3 rabbits and the eyes were left unwashed in the remaining 6 rabbits. Fyrquel EHC (trixylenyl phosphate) produced mild to moderate conjunctival irritation in all tested rabbits. All irritation cleared within 24 hours (REACH).

In general, triaryl phosphate esters are non-irritating to eyes (Weiner and Jortner, 1999). TCP and other substituted aryl phosphates are at most slight irritants in studies in rabbits (NICNASa; NICNASb).

Sensitisation

Skin Sensitisation

No data are available for the substances. In general, triaryl phosphate esters are non-sensitising to skin (Weiner and Jortner, 1999). Based on data for other triaryl phosphate esters, TCP (CAS No. 1330-78-5), cresyl diphenyl phosphate (CAS No. 26444-49-5) and triphenyl phosphate (TPHP; CAS No. 115-86-6) (NICNASa; NICNASc; NICNASd), the assessed substances are not expected to be potent skin sensitisers.

Repeated Dose Toxicity

Oral

Based on the adrenal effects seen in a repeated oral dose toxicity study with TXP in rats, hazard classification for repeated oral toxicity is recommended for the substances (see ***Recommendation*** section). Systemic effects observed in the adrenals are consistent with those observed with other substituted aryl phosphate esters (NICNASa; NICNASb; NICNASc).

In an OECD TG 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test), SD rats (11/sex/dose) were orally (gavage) treated with 0 (vehicle control), 25, 200 or 1000 mg/kg bw/day of Phosflex TXP (trixylyl phosphate) in a vehicle of corn oil. Rats were treated with the substance for minimum of 33 days for males and 48 days for females. The treatment did not cause any clinical signs of toxicity or loss of body weight in parental animals. Significantly increased absolute and relative adrenal weights were reported at 200 mg/kg bw/day and above. The absolute and relative liver weighs were increased in both sexes at 1000 mg/kg bw/day and in males at 200 mg/kg bw/day. Treatment-related histological findings of diffuse cytoplasmic vacuolation were also reported in the adrenals in males at all dose levels and females at 200 and 1000 mg/kg bw/day. Liver histopathological changes were also observed in mid and high dose females. Reproductive organs including the testes and ovaries were also affected (see ***Reproductive and Developmental Toxicity*** section). The incidence and severity of all histological changes was decreased in the recovery groups, indicating reversibility of the effects. A lowest observed adverse effect level (LOAEL) is 25 mg/kg bw/day. A no observed adverse effect level (NOAEL) could not be established (ECHA, 2013).

Dermal

No data are available.

Inhalation

No data are available.

Genotoxicity

Based on the available in vitro studies with TXP and the weight of evidence from other substituted aryl phosphates (NICNASa; NICNASb; NICNASc), the assessed substances are not expected to be genotoxic.

In an OECD TG 471 (bacterial reverse mutation assay), *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 and *Escherichia coli* tryptophan auxotroph WP2wvrA were exposed to 33.3, 100, 333, 1000, 3330 and 5000 µg of Phosflex TXP per plate in the presence or absence of the metabolic activation (S9 mix). No mutagenicity was observed at any of the concentrations assessed, either in the presence or absence of metabolic activation (REACH).

In an OECD TG 473 (in vitro mammalian chromosome aberration test) study, Chinese hamster ovary (CHO) cells were exposed up to 240 µg of Phosflex TXP per plate in the presence or absence of the metabolic activation (S9 mix). No increases in structural or numerical chromosomal aberrations were reported in CHO cells with and without metabolic activation (REACH).

Carcinogenicity

No information is available for the substances in this assessment. Based on data for TCP (NICNASa) the substances are not expected to be carcinogenic.

Reproductive and Developmental Toxicity

The substance TXP (CAS No. 25155-23-1) is classified as hazardous, with the hazard category ‘Reproductive toxicity – category 1B’ and hazard statement ‘H360F (May damage fertility)’ in the Hazardous Chemical Information System (HCIS) (Safe Work Australia). The available data for this chemical and the weight of evidence from substituted aryl phosphate esters (NICNASa; NICNASb; NICNASc), support this classification for all the substances (see ***Recommendation*** section).

In an OECD TG 422 (combined repeated dose toxicity study with the reproduction/developmental toxicity screening test), SD rats (11/sex/dose) were orally (gavage) treated with 0 (vehicle control), 25, 200 or 1000 mg/kg bw/day of Phosflex TXP (commercial TXP) in a vehicle of corn oil. Rats were treated with the substance two weeks prior to mating, during mating and throughout gestation and lactation. The treatment did not cause any clinical signs of toxicity or loss of body weight in parental animals. The percentage of female rats that successfully delivered pups was 100 % in the control and 25 mg/kg bw/day groups, and 18% and 0% in the 200 and 1000 mg/kg/day groups, respectively. Litter size, survival and offspring body weight were unaffected by treatment at 25 mg/kg bw/day. Absolute and body weight relative testes and epididymides weights were significantly reduced at the highest dose. Absolute and relative ovary weights were significantly elevated in the 200 and 1000 mg/kg bw/day groups. Treatment-related histological findings in the testes, epididymides, and ovaries were reported at all doses. Lesions consisted of degeneration of the germinal epithelium of the testes and sloughing of cells in the epididymal lumen. Distinct mild diffuse hyperplasia of the interstitial cells was reported in ovaries. Therefore, based on treatment-related histological findings in reproductive organs, a LOAEL of 25 mg/kg bw/day was established for reproductive toxicity. A NOAEL for the reproductive toxicity was not established in this study (ECHA, 2010).

Other Health Effects

Neurotoxicity

Some triaryl phosphate esters cause organophosphate induced delayed neuropathy (OPIDN), a neurodegenerative disorder characterised by a delayed onset of prolonged ataxia and upper motor neuron spasticity. Except for tri-para-ethyl phosphate (e.g. CAS No. 3820-69-7), the neurotoxic triaryl phosphate esters have at least one ortho-alkylphenyl ester group (NICNASc). The tri-para-ethyl and ortho-alkylphenyl phosphate esters can be metabolised into neurotoxic metabolites (see ***Toxicokinetics*** section).

The assessed substances may contain both ortho-methylated and para-ethylated phenyl phosphate esters. While ortho-methylated aryl phosphate esters are neurotoxic (NICNASc), further substitution of the phenyl ring (as with xylyl phosphate esters) significantly reduces neurotoxic potential of the substances (see ***Toxicokinetics*** section).

These substances are not as potent neurotoxins as cresyl phosphates. Based on the available data, the substances have potential to cause neurotoxicity only at very high exposure levels. The neurotoxicity of the assessed substances is expected to depend on the proportion of tri-para-ethylated aryl phosphates and the presence of an ortho-cresyl fraction as an impurity (Bondy et al., 1960).

Dimethyl phenyl (xylyl) phosphate esters

The xylyl phosphate esters are generally not neurotoxic when free from ortho-alkylated phenols (Bondy et al., 1960) and the purified dimethylphenyl isomers do not cause neurotoxicity. Commercial TXP formulations, may have potential to cause neurotoxicity at very high exposure levels, which may be dependent on the impurities in the commercial formulation.

Esters of 2,6; 2,4; 2,5; 2,3; 3,5 and 3,4-dimethylphenol were reported to be non-toxic to hens when given at a cumulative dose of 2500 mg/kg bw (5x500 mg/kg bw) (Bondy et al., 1960). The symmetrical tris-2,6-dimethylphenyl phosphate ester and tris-2,4-dimethylphenyl phosphate ester did not cause ataxia in hens dosed at 1000 mg/kg bw/day, twice a day for six days (Johannsen et al., 1977). In unsymmetrical aryl phosphate esters the presence of a 3:5-dimethylphenyl group is reported to reduce the toxicity of any ortho-susbtituted phenyl groups considerably (Bondy et al. 1960)

Clinical signs of ataxia in hens were observed with one commercial formulation at a dose of 600 mg/kg bw but were only observed in other commercial formulations at much higher doses (Weiner and Jortner, 1999). TXP, purified to remove both ortho-cresol and ortho-ethylphenol, produced no toxic effects in hens exposed to two doses of 625 mg/kg bw in a single day. However, a cumulative dose of 2500 mg/kg bw (5x500 mg/kg bw) caused effects in 4 out of 12 animals (Bondy et al, 1960). TXP, purified to remove both ortho-cresol, ortho-ethylphenol and ortho-propylphenol did not cause neurotoxic effects in a range of animals up to very high doses (Bondy et al, 1960).

In a non-guideline study, White Leghorn hens received daily oral doses (gavage) of 2000 mg/kg bw of undiluted TXP (test substance E-97001, purity not specified). Hens receiving 60 mg/kg bw/day of TOCP or corn oil daily for five days were used as positive and negative controls, respectively. The NTE activity was completely inhibited (100% inhibition relative to controls) in the TOCP treated hens (positive controls). The mean NTE inhibition in hens treated with trixylenyl phosphate was 84 %. This is above the 70 % criterion for peripheral neuropathy, supporting the conclusion that the substances may cause neurotoxicity at very high doses (REACH).

Ethylphenyl phosphate esters

In a non-guideline study, 6 adult chickens (Light Sussex cross with Rhode Island Red or White Leghorn) of both sexes received either a cumulative dose of 2500 mg/kg bw (5x500 mg/kg bw) or a single dose of 200 mg/kg bw of tri-para-ethylphenyl phosphate ester. All birds treated with tri-para-ethylphenyl phosphate ester were paralysed. However, the mixed esters containing one or two para-ethylphenyl groups were not neurotoxic (unless containing ortho-cresyl isomers). When adult chickens received cumulative oral doses up to 7000 mg/kg or a single oral dose of 2500 mg/kg bw of mono-para-ethylphenyl dixylyl phosphate ester (n=3/dose group), no signs of neurotoxicity were reported. No signs of neurotoxicity were reported with di-para-ethylphenyl mono-para-cresyl phosphate ester when given to 4 chickens at a cumulative dose of 2500 mg/kg bw or a single dose of 1000 mg/kg bw. This demonstrated that the tri-para-ethylphenyl phosphate content, but not the total content of para-ethylphenol is critical for the neurotoxic potential of the assessed substance (Bondy et al., 1960).

The tri-ortho- or meta-ethyl phenyl phosphate esters were not neurotoxic. In a non-guideline study, adult hens (approximately 10/group) received cumulative oral dose (within 6 days) of 12000 mg/kg bw of tri-ortho-ethylphenyl phosphate ester or 120000

mg/kg bw of tri-meta-ethylphenyl phosphate ester and observed for 42 days. No signs of neurotoxicity (behavioural or histological) were reported (Johannsen et al., 1977).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation are systemic long-term effects and reproductive toxicity. The substances may also have potential for neurotoxicity but only at very high exposure levels.

Public Risk Characterisation

Given the uses identified for these substances, there is a low likelihood that the public will be exposed significantly. The public could come into contact with articles or coated surfaces containing the chemicals, although it is expected that the chemicals will be bound within the articles or coated surfaces. Some of the chemicals could be released from articles through e.g. abrasion or dissolution. Dust originating from indoor environments (e.g. houses, offices, stores) is considered as a major source of human exposure to flame retardants. Aryl phosphate ester flame retardants are commonly detected in house dust (Wu et al., 2016). However, while these substances are not specifically analysed in Australia, they are not expected to be readily released from articles due to low vapour pressure (ECHA, 2013) and the levels of aryl phosphate esters in dust are generally low. TXP has been reported in dust measurements overseas with median dust concentrations <100 ng/g of dust (Kademoglou et al, 2017). Using a conservative assumption, dust intake has been estimated to be 200 mg/d (enHealth, 2012) and maximum levels detected in dust in UK houses, daily intake for toddlers was 8.7 ng/kg bw/day. This gives a margin of exposure of >2000000. Whilst there is particular concern regarding the potential risk of oral exposure to flame retardants in toddlers/children, due to hand-to-mouth behaviour and from sucking on polyurethane toys containing certain phosphate flame retardants (NICNASe), TXP is not identified as a common flame retardant used in polyurethane foam toys (US EPA, 2015).

The available data indicate that, although public exposure could be widespread via inhalation and dermal routes, it is at a very low level and the risk of adults and children being exposed to levels of the substances that would lead to adverse health effects, is very low. Should further information to better characterise exposure become available, further assessment may be required.

Occupational Risk Characterisation

During handling of the substances, dermal, oral and inhalation exposure of workers 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, these substances could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, oral and inhalation exposure are implemented. These chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

The data available support an amendment to the hazard classification in the HCIS (Safe Work Australia) (see ***Recommendation*** section).

Workers in environments with large numbers of products containing the chemical, such as computer stores, could be exposed to dust containing high levels of the chemical (Kademoglou et al., 2017). However, based on available data, the risk of being exposed to levels of the substances that would lead to adverse health effects is very low. Should further information to better characterise exposure become available, further assessment may be required.

NICNAS Recommendation

Assessment of the substances is considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory. No further assessment is required unless new information regarding the uses of the substances in cosmetic or domestic products/scenarios or information to characterise public and worker exposure from its use in articles in Australia becomes available.

Regulatory Control

Work Health and Safety

The substances are recommended for classification and labelling aligned with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

The recommended classification for repeat dose toxicity (H373) applies to all substances in the group. The substance TXP (CAS No. 25155-23-1) is currently classified for reproductive toxicity (H360F) (Safe Work Australia). This classification should also apply for other substances for the other substances (CAS Nos 29660-68-2 and 68952-33-0).

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]
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)

[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 substances should be used according to the instructions on the label.

Advice for industry

Control measures

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

- using closed systems or isolating operations;

- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

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

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

Obligations under workplace health and safety legislation

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

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

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

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

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

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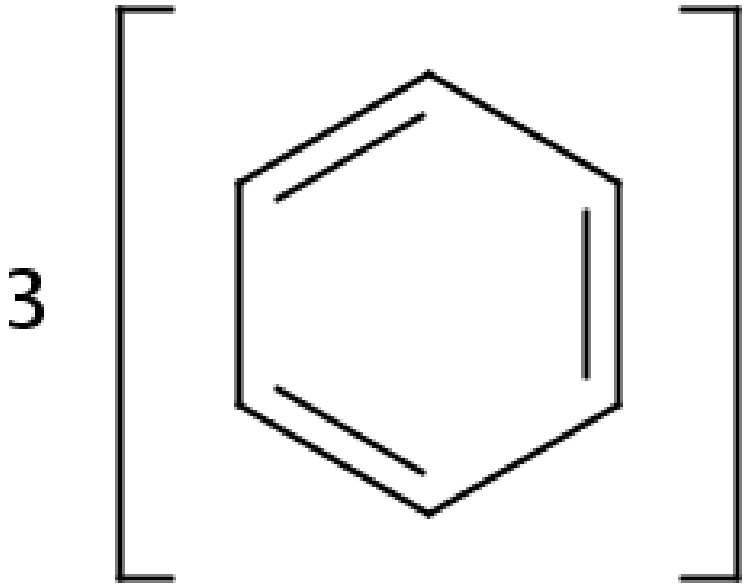
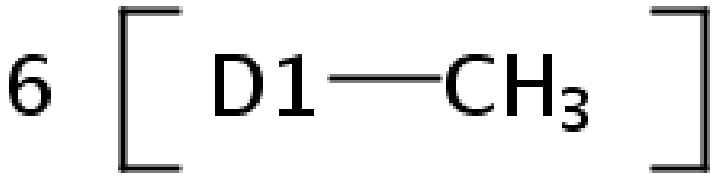
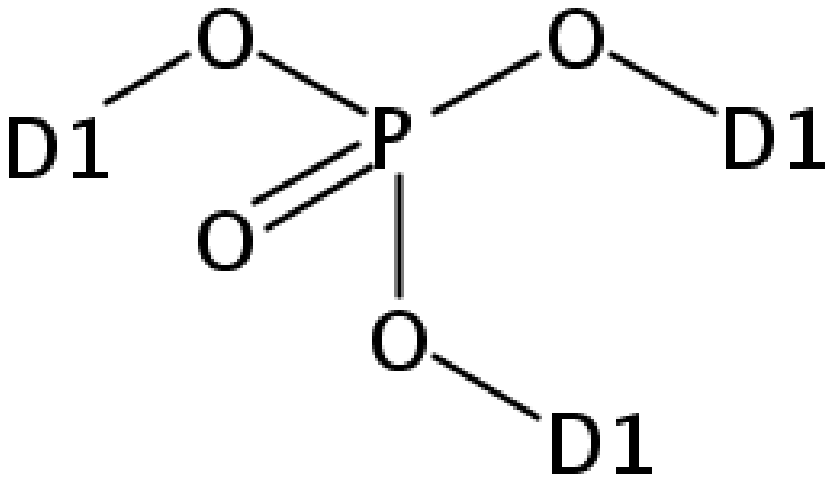
Last Update 02 March 2018

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phenol, dimethyl-, phosphate (3:1)** trixylyl phosphate TXP tri-dimethyl phenyl phosphate phenol, dimethyl-, 1,1',1''-phosphate
CAS Number	25155-23-1
Structural Formula	

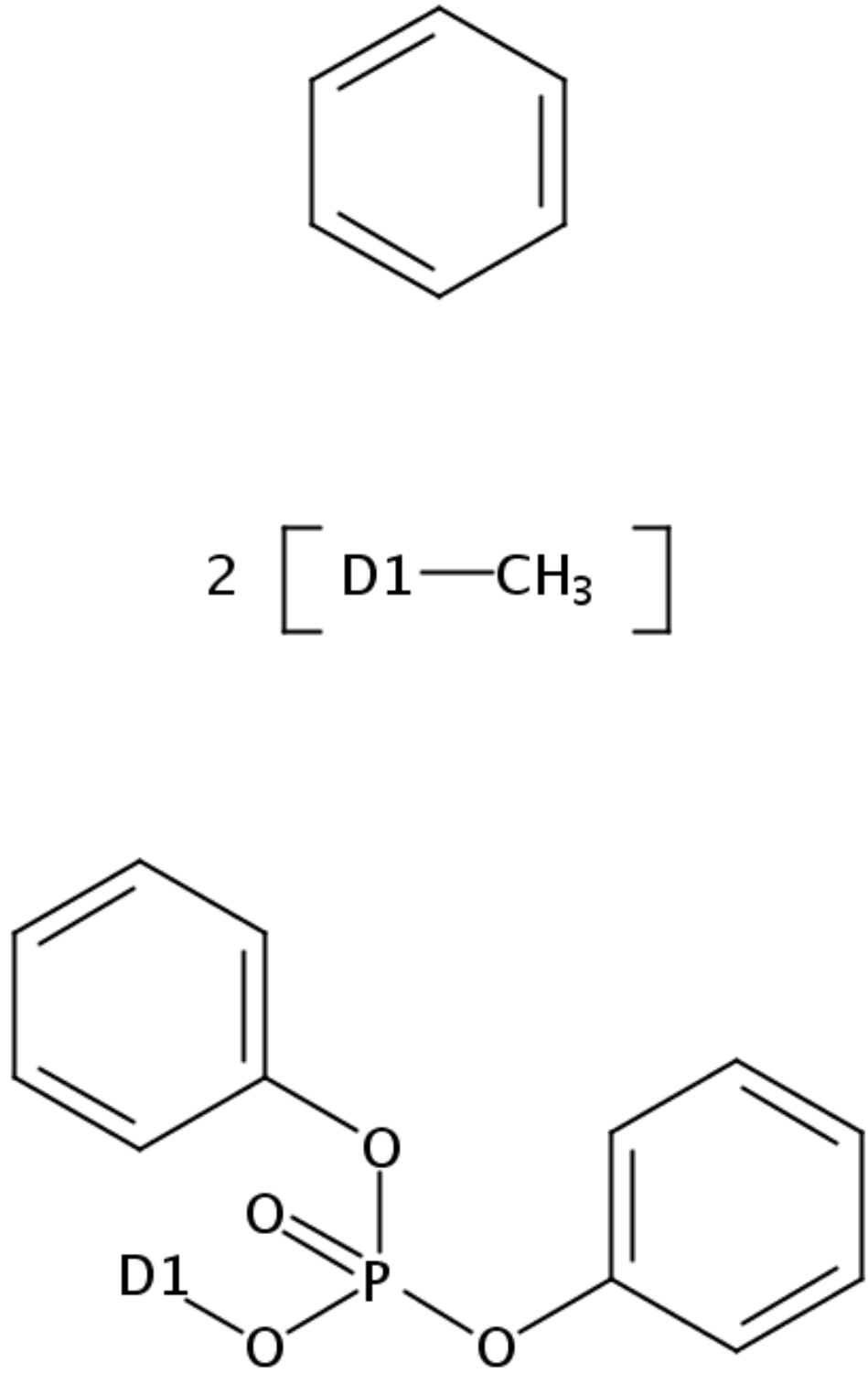






Molecular Formula	C24H27O4P

Molecular Weight	410.45

Chemical Name in the Inventory and Synonyms	**Phosphoric acid, dimethylphenyl diphenyl ester** diphenyl xylyl phosphate
CAS Number	29660-68-2
Structural Formula	

Molecular Formula	C20H19O4P
Molecular Weight	354.34

Chemical Name in the Inventory and Synonyms	**Tar acids, cresylic, C8 rich, phosphates** phosphate esters of coal tar or petroleum derived cresylic acids
CAS Number	68952-33-0
Structural Formula	
Molecular Formula	Unspecified
Molecular Weight	Unspecified

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