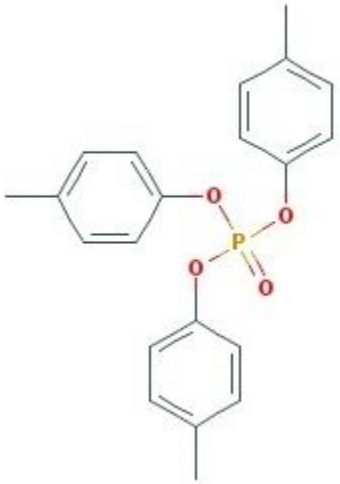
TRIPARACRESYL PHOSPHATE

CAS number: 78-32-0

Synonyms: TPCP; Phosphoric acid, tris(4-methylphenyl)ester; Tri-p-tolyl phosphate

Molecular formula: $C_{21}H_{21}O_4P$

Chemical structure[1]:



TLV-TWA, 0.05 mg/m^3 (0.003 ppm), Inhalable fraction and vapor

TLV® Recommendation

A TLV-TWA of 0.05 mg/m^3 (0.003 ppm), inhalable fraction and vapor, is recommended for occupational exposure to triparacresyl phosphate (TPCP), the para-isomer of tricresyl phosphate (TCP). This value is intended to minimize the potential for any unwanted effects and notes the difference between this para-isomer and the ortho-isomer (TOCP) whose TLV of 0.02 mg/m^3 is based on cholinergic effects and central and peripheral neuropathies. Unlike TOCP, this chemical does not have the potent neurologic properties of the ortho-isomer and is generally considered to be less active or inactive in this regard.[2] Human information is very limited and no reliable quantitative data are available, hence the TLV is derived from data on animal species. The toxicity database for this isomer is limited, but acute studies show a lack of neurotoxicity in hens[3,4] and this effect is not reported in cats,[5] the 2 species used in establishing the TLV for TOCP based on its neurotoxic potential. No neurotoxicity or damage to other tissues was seen when rats were fed 1,000 mg/kg of a 35% to 40% mixture of TPCP (350 to 400 mg/kg as TPCP) for 3 months.[6]

Chronic and subchronic studies in rats and mice with a mixture that contained only 4% TPCP (and 1% TOCP) does not appear to be specific enough for this isomer to use as a basis for airborne control, but no signs of neurotoxicity were seen in those studies. However, in an oral dosing study in mice, degeneration of the spinal cord and sciatic nerve were seen at a dose of 16 mg/kg TPCP (2,100 ppm of the 4% mixture). No evidence of neuropathy was seen in rats dosed orally for 13 weeks with up to 32 mg/kg TPCP (800 mg/kg of the 4% mixture).[7] In 2-year feeding studies, no signs of neurotoxicity were seen in either rats fed up to 1 mg/kg (25 mg/kg of the mixture) or mice fed up to 1.2 mg/kg (30 mg/kg of the mixture).[7] In both species and in both the 13-week and the 2-year studies, cytoplasmic vacuolation of the adrenal gland was seen at the lowest doses tested, 0.16 mg/kg in the rat and 0.3 mg/kg in the mouse.[7] Female rats, but not mice, had ovarian interstitial cell hyperplasia when given doses of 0.6 mg/kg or greater for 2 years, but not when the dose was discontinued after 6 months and the rats were sacrificed after 2 years.[7] It should be noted that TPCP made up

4% of the mixture and that the responses, or lack of responses, was to the entire mixture. Interactions, enhancing or suppressing the activity of the individual components, cannot be ruled out.

The TLV-TWA of 0.05 mg/m^3 is based on the lowest observed effect level seen in the animal studies (0.15 mg/kg and assumes complete absorption by a 70-kg worker inhaling 10 m^3 per work shift, 1 mg/m^3) and reflects the quality of the database, the lack of quantitative human information, and the reliance on studies involving TPCP as a mixture of tricresyl phosphate (TCP), not the pure compound. For reference, this isomer does not appear to share the neurotoxic properties of the ortho-isomer TOCP (whose TLV-TWA is 0.02 mg/m^3).

A Skin notation is not recommended because TPCP, by analogy to TOCP, is expected to be well absorbed through the skin, but does not appear to produce neurologic damage. Sufficient data were not available to recommend DSEN, RSEN, or carcinogenicity notations, but no increase in neoplasms was seen in either mice or rats after 2 years of feeding a mixture that contained 4% TPCP.[7]

TLV Basis

Adrenal gland damage; female reproductive system damage.

Chemical and Physical Properties

TPCP has a very slightly aromatic odor and is a colorless crystalline solid.

Table 1. Chemical and Physical Properties of Triparacresyl Phosphate (TPCP)[8]

Property	TPCP
Molecular weight	368.36
Specific gravity	1.247
Melting point	170°F (77°C) to 172.4°F (78°C)
Boiling point	471°F (244°C) at 35 torr
Vapor pressure	4.9×10^{-7} at 25°C
Saturated vapor concentration	0.00971 mg/m^3
Flash point	Not available
Explosive limits	Not available
Autoignition temperature	Not available
Solubility	Very slightly soluble in water; soluble in ethanol, ethyl ether, benzene, and carbon tetrachloride
Octanol/water partition coefficients	log K_{ow} = 6.34
Conversion factors at 77°F (25°C) and 760 torr	1 ppm = 15 mg/m^3; 1 mg/m^3 = 0.066 ppm

TPCP is the para-isomer of TCP. Commercial TCPs contain around 4% to 5% TPCP. These commercial TCPs are a heterogeneous mixture of isomers and aryl phosphate congeners, known for many years to induce delayed neurotoxicity (organophosphate-induced delayed neurotoxicity [OPIDN]). Although TOCP has been considered the component primarily responsible for OPIDN, it is now clear that other constituents, particularly the mono-o-esters, are also neurotoxic, perhaps even as or more potent than TOCP. In general, the toxicity of a particular brand of TCP is related to its content of o-phenolic residues with the maximal potential reached when the o-phenolics are 33% of the mix.[9]

Major Sources of Occupational Exposure

TPCP is used as a plasticizer in vinyl plastic manufacture. It is also used as a flame retardant, as a solvent for nitrocellulose, in cellulosic molding compositions, as an additive to high-pressure lubricants, as a nonflammable fluid in hydraulic systems, as a lead scavenger in gasoline, and to sterilize certain surgical instruments. With the other cresyl phosphate isomers and phthalates, it is used in flexible polyvinyl chloride (PVC) with typical applications being vinyl tarpaulins, mine conveyer belts, air ducts, cable insulation, and vinyl films.

Human Studies

The para-isomer of cresyl phosphate is relatively inactive compared to the ortho-isomer. Chronic symptoms following inhalation and cutaneous absorption include hyperhydrosis, hypotension, general fatigue, irritability, and paresthesia.[10] It is not clear what role this isomer plays in this collection of symptoms, but it is clear that the ortho-isomer is considerably more active than the para-isomer (or the meta-isomer). A case report on a worker engaged in the manufacture of both the meta- and para-isomers showed anorexia, nausea, and

aching of the legs. The final product contained only 1% TOCP, but 6% to 10% was present as a contaminant during manufacture and the TPCP content was not reported.[11]

Animal Studies

Acute

TPCP is low in acute oral toxicity, with LD_{50} values of greater than 1,000 mg/kg in cats, 2,000 mg/kg in hens, and 12,800 mg/kg in rats.[12] No deaths occurred in rats given 3,000 mg/kg or cats given 200 mg/kg subcutaneously.[11]

Rabbits given single oral doses of either 500 or 700 mg/kg showed no evidence of delayed paralysis.[13] No signs of delayed neurotoxicity were seen in hens given a single oral dose of TPCP.[14] No inhibition of brain neurotoxic esterase was seen either after *in vivo* treatment of hens with a single oral dose of 1,000 mg/kg or *in vitro* following incubation of hen brains with 100 µM.[4]

Subchronic

A mixed isomer preparation of TCPs containing 4% of the para-isomer was tested. Rats fed 900, 1,700, 3,300, 6,600, and 13,000 ppm (equivalent to about 2.4, 4.8, 9, 17, and 30 mg/kg TPCP, respectively) for 13 weeks showed body weight gain decreased at the 3 highest feeding levels. All TPCP-fed rats had changes in the adrenal glands (cytoplasmic vacuolation) and ovaries (hyperplasia and inflammation of interstitial cells). In rats fed 6,600 and 13,000 ppm, kidney necrosis and atrophy of the seminiferous tubules were detected.[7] In a similar study in which rats were given oral doses of a 4% TPCP mixture by gavage of 50, 100, 200, 400, and 800 mg/kg for 13 weeks (doses of 2, 4, 8, 16, and 32 mg/kg TPCP, respectively), body weights from 200 mg/kg were lower than that of the controls. Adrenal gland cytoplasmic vacuolation and ovarian interstitial cell hypertrophy were seen at all tested doses. Atrophy of the seminiferous tubules occurred in males given 400 or 800 mg/kg. No neurobehavioral changes were detected.[7] In a similar pair of mouse studies, feeding of 250, 500, 1,000, 2,100 and 4,200 ppm (equivalent to about 2, 4, 8, 16 and 40 mg/kg TPCP, respectively) for 13 weeks produced cytoplasmic vacuolation in the adrenals in all groups. Hyperplasia of the gall bladder was seen at dietary levels of 500 ppm and greater. Axonal degeneration occurred in both sexes exposed to 2,100 ppm or greater and renal tubule regeneration was seen in all males fed 4,200 ppm.[7] In the oral dosing portion, mice were given doses of 50, 100, 200, 400, or 800 mg/kg (equivalent to 2, 4, 8, 16 and 32 mg TPCP/kg, respectively) for 13 weeks. Body weights of mice receiving 200 mg/kg or higher were reduced. Vacuolation of the adrenal glands was seen in all groups, with the severity increasing with dose. All groups of female mice showed ovarian interstitial cell hypertrophy. Degeneration of the spinal cord and sciatic nerve occurred in mice given doses of 100 mg/kg (females only) or greater (both sexes from 200 mg/kg). Hind limb grip strength of males given 200 mg/kg and greater was significantly reduced.[7]

Rats fed a mixture containing 35% to 40% TPCP for 3 months at doses of 30, 100, 300, and 1,000 mg/kg (equivalent to 10-12, 35-40, 100-120, and 350-400 mg/kg TPCP, respectively) showed no changes in tissues or organs on histopathologic examination.[6]

Chronic/Carcinogenic

A preparation of TCP containing 4% of the para-isomer was tested in a 2-year feeding study. Rats were fed dietary levels of 75, 150, 300, or 600 ppm (equivalent to daily TPCP doses of about 0.16, 0.32, 0.6, and 1 mg/kg, respectively). Rats were fed 600 ppm for 22 weeks then received control food for the duration of the study. Body weights, clinical observations, and survival of TPCP-treated rats were similar to those of the controls. There were no chemically related increased incidences of neoplasms in these rats. Adrenal gland cytoplasmic vacuolation was seen at levels of 150 ppm or higher. Ovarian interstitial cell hyperplasia occurred in female rats exposed for 2 years at 300 ppm for 22 weeks and allowed recovery to 2 years.[7] In a 2-year feeding study, mice were fed dietary levels of 60, 125, or 250 ppm (equivalent to daily TPCP doses of about 0.3, 0.6, and 1.2 mg/kg, respectively). Body weights, clinical observations, and survival of TPCP-treated mice were similar to that of the controls. There were no chemically related increased incidences of neoplasms in these mice. An increased incidence of ceroid pigmentation of the adrenal cortex was seen in females fed 250 ppm, and liver changes including clear cell foci, fatty change, and ceroid pigmentation were seen in males fed either 125 or 250 ppm; hind and forelimb grip strength was not affected.[7]

Genotoxic

Testing a preparation of TCP containing 4% TPCP was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537. It did not induce chromosomal aberrations or sister-chromatid exchanges

in cultured Chinese hamster ovary cells. These tests were conducted both with and without S9 metabolic activation.[7]

Reproductive and Developmental Toxicity

No testicular damage was seen in rats given oral doses of 100 mg TPCP/kg for 14 days.[15]

A mixture of TCP isomers (containing less than 9% TOCP, the remainder being a mixture of TCP and trimetacresyl phosphate [TMCP; in which the TPCP content was not specified but was a minor component] and other tricresyl isomers) was given to male rats (100 or 200 mg/kg) and female rats (200 or 400 mg/kg) orally for 56 days before mating (males) or 14 days (females). The number of females delivering live young was reduced in both low- and high-dose groups, along with litter size and pup viability. Pup weights, structure, and developmental landmarks were unaltered. Both male and female reproductive organs showed damage when examined histopathologically.[16] Again using a mixture of TCP isomers (74.9% pure or mixed isomers with <0.1% pure tri-ortho cresyl, 20.6% pure meta-cresyl, and 3.9% pure para-cresyl phosphate) in a continuous breeding study in mice receiving dietary levels of 500, 1,000, or 2,000 ppm over 98 days, though the fertility indices were not changed, the number of females delivering live young and their weights were reduced in a dose-related manner. Males showed seminiferous tubule atrophy and decreased testes and epididymal weights, but no changes were seen in the female reproductive tract.[17]

Toxicokinetic/Toxicodynamic Studies

A single oral dose of 2, 20, or 200 mg/kg TPCP or a single intravenous dose of 20 mg/kg TPCP was given to rats and was well absorbed. At the 2 lower doses, the primary route of excretion was the urine, whereas at the higher doses, the primary route was the feces. A dose-dependent biliary excretion that represented an approximate doubling between doses of 2 and 20 mg/kg was seen. The percentage appearing in the feces was less than that excreted in the bile, suggesting substantial enterohepatic recycling. TPCP was rapidly distributed to the muscle and liver, then redistributed to the adipose tissue and skin. There was no tendency of TPCP to bioaccumulate in specific organs or tissues. Although dermal absorption was not evaluated, a single dermal application of the ortho-isomer, TOCP, was well absorbed and the similarity of structure and physical properties makes it likely that the para-isomer will be well absorbed through the skin.[7]

In a previous experiment, 41% of the radiolabel was excreted in the urine and 44% in the feces in 7 days. The expiratory excretion as CO_2 was 18% in the first 3 days. On days 1, 3, and 7 days, radioactivity was high in the adipose tissue, liver, and kidney. TPCP was distributed to the fatty tissues, moderately metabolized to a variety of oxidation and dearylation products, which were then excreted in the urine, feces, bile, and expired air. Intestinal microflora appeared to play an important role in degrading biliary metabolites to $^{14}CO_2$ through the enterohepatic circulation in rats.[18]

The major metabolites found in the urine were p-hydroxybenzoic acid, di-p-cresyl phosphate (DCP), and p-cresyl p-carboxyphenyl phosphate (1coDCP). Biliary metabolites were DCP, 1coDCP, and the oxidized trimesters, di-p-cresyl p-carboxyphenyl phosphate and p-cresyl di-p-carboxyphenyl phosphate. The main fecal metabolite was unchanged TPCP and the others were those found in the bile.[18]

TLV® Chronology

Table 2. TLV Chronology: *Triparacresyl Phosphate*

Date	Action	Determinant	TLV
2016	Proposed	TLV-TWA	0.05 mg/m^3 (IFV)
2024	Adopted	TLV-TWA	0.05 mg/m^3 (IFV)

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