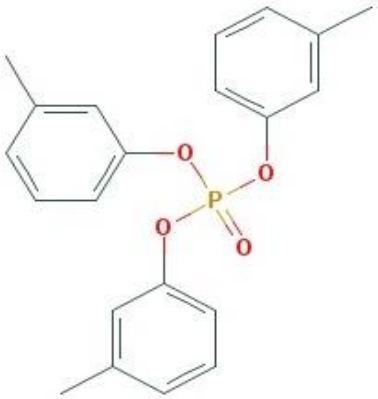
TRIMETACRESYL PHOSPHATE

CAS number: 563-04-2

Synonyms: TMCP; Phosphoric acid, tris(3-methylphenyl)ester; Tri-m-tolyl phosphate

Molecular formula: C21H21O4P

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, inhalable fraction and vapor, is recommended for occupational exposure to trimetacresyl phosphate (TMCP), the meta-isomer of tricresyl phosphate (TCP). This value is intended to minimize the potential for any unwanted effects and notes the difference between this meta-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 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 also quite limited, but acute studies show a lack of neurotoxicity in the chicken[3,4] and cat,[5] the 2 species used in the establishment of the TLV for TOCP (based on its neurotoxic potential). Chronic and subchronic studies in rats and mice with a mixture containing 21% TMCP (and 1% TOCP) found effects on the adrenal gland at doses as low as 1.7 mg/kg in the rat (4 mg/kg of the 21% mixture) and 6 mg/kg in the mouse (7 mg/kg of the mixture) with no effect seen at 0.8 mg/kg in the rat and 3 mg/kg in the mouse. Hyperplasia and inflammation of ovarian interstitial cells were seen in rats at all doses tested in the 13-week study and in rats fed 150 ppm, but not 300 ppm, in the 2-year study. Ovarian effects were not seen in mice.[6] No signs of neurotoxicity were seen in those studies, but in oral dosing studies in mice, degeneration of the spinal cord and sciatic nerve were seen at a dose of 21 mg/kg TMCP (100 mg/kg of the 21% mixture). No evidence of neuropathy was seen in rats dosed orally for 13 weeks, with up to 170 mg/kg TMCP (800 mg/kg of the 21% mixture).[6] In the 2-year feeding studies, no signs of neurotoxicity were seen in either the rat, fed up to 5 mg/kg (25 mg/kg of the mixture), or the mouse, fed up to 6 mg/kg (30 mg/kg of the mixture). In both rodent species and in both the 13-week and 2-year studies, cytoplasmic vacuolation of the adrenal gland was seen: at the lowest doses tested in the 13-week study (10 to 12 mg/kg) and at 1.7 mg/kg (but not at 0.8 mg/kg) in the rat and 6 mg/kg (but not at 3 mg/kg) in the mouse. Female rats, but not mice, had ovarian interstitial cell hyperplasia when given doses of 3.2 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.[6] It should be noted that TMCP comprised 21% of the tested mixture and that the responses, or lack of responses, were to the entire mixture. Interactions, enhancing or

suppressing the activity of the individual components, cannot be ruled out. No neurotoxicity or damage to other tissues was seen when rats were fed 1,000 mg/kg of a 60% to 65% mixture of TMCP (600 to 650 mg/kg) for 3 months.[7]

The TLV-TWA of 0.05 mg/m^3 is based on the lowest observed effect level seen in the animal studies (0.8 mg/kg and assumes complete absorption by a 70-kg worker inhaling 10 m^3 per work shift, 5.6 mg/m^3) and reflects both the quality of the database, the lack of quantitative human information, and the reliance on studies involving TMCP as a mixture of tricresyl phosphate, not the pure compound. For reference, this isomer does not appear to share the neurotoxic properties of the ortho-isomer TOCP (TLV-TWA of 0.02 mg/m^3).

A Skin notation is not recommended because TMCP, by analogy to TOCP, can be well absorbed through the skin, but does not appear to produce neurologic damage, though no tests in animals using the dermal route were found. Sufficient data were not available to recommend DSEN, RSEN, or carcinogenicity notations, however, no increase in neoplasms was seen in either mice or rats after 2 years of feeding a mixture that contained 21% TMCP (and approximately 1% TOCP).[6]

TLV Basis

Adrenal gland damage; female reproductive system damage.

Chemical and Physical Properties

TMCP is practically odorless and is a waxy solid that is colorless or pale yellow.

Table 1. Chemical and Physical Properties of Trimetacresyl Phosphate (TMCP)

Property	TMCP
Molecular weight	368.36
Specific gravity	1.150
Melting point	77.9°F (25.5°C)
Boiling point	260°C at 15 torr
Vapor pressure	7.8×10^{-7} at 25°C
Saturated vapor concentration	Not available
Flash point	Not available
Explosive limits	Not available
Autoignition temperature	Not available
Solubility	Not soluble in water; slightly soluble in ethanol, soluble in ethyl ether and very soluble in 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

TMCP is the meta-isomer of tricresyl phosphate (TCP). Commercial TCPs contain around 21% TMCP; manufacturing precautions have been used to reduce the concentrations of the ortho-isomer (TOCP) found in historical preparations that contained upwards of 20% TOCP.[2] These commercial tricresyl phosphates 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 tricresyl phosphate is related to its content of *o*-phenolic residues, with the maximal potential reached when the *o*-phenolics are 33% of the mix.[8]

Major Sources of Occupational Exposure

TMCP is used as a plasticizer in vinyl plastic manufacture. It is also used as a flame-retardant, 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. It has also been used as an air filter medium, for waterproofing, and as a heat exchange medium.

Human Studies

Signs of TCP poisoning include hyperhydrosis, hypotension, general fatigue, irritability, and paresthesia in the limbs, with the ortho-isomers thought to be responsible for the effects.[9] 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 TMCP content was not reported.[10] The commercial product, which contains around 20% of this isomer (and only 1% of the ortho-isomer, TOCP), has been shown to affect the nervous system, but the meta- and para-isomers appear to be relatively inactive.[2] Again, the limited data here suggest that the neurologic effects of TCP are due to the presence of the ortho-isomer, but there is not enough convincing evidence for the lack of effect of the meta- and para-isomers. Patch testing on an individual showing irritation from spectacle frames had a positive response to a 0.5% solution of TMCP.[11]

Animal Studies

Acute

TMCP is low in acute oral toxicity, with LD_{50} values greater than 3,000 mg/kg in the rabbit and greater than 2,000 mg/kg in the chicken.[12] Cats survived a single oral dose of 300 mg/kg and showed no clinical signs of neurotoxicity.[5] No deaths occurred in rats given a single oral dose of 3,000 mg/kg.[10]

Chickens given a single dose of TMCP (following a protective dose of 5 mg/kg atropine) remained normal with no signs of a response during a 35-day postdosing observation period. Brain and spinal cord cyclic nucleotide phosphohydrolase (a biochemical indicator of delayed neurotoxicity) was not affected nor did the ataxia seen with TOCP occur in these hens. Sciatic nerve damage was not detected.[3] A second study using a single oral dose of 200 mg/kg again showed no delayed (or any) neurotoxicity and concentrations of 6 trace elements including calcium were unaffected.[13] A dose of 1,000 mg/kg to chickens did not affect brain neurotoxic esterase, while a single dose of 10 mg/kg TOCP produced a 41% inhibition.[4] Thus, it is clear that this isomer does not share the neurotoxic properties of the ortho-isomer, TOCP.

Subchronic

A mixed isomer preparation of TCP containing 21% of the meta-isomer was tested. Rats fed 900, 1,700, 3,300, 6,600, and 13,000 ppm (equivalent to about 12.5, 25, 47, 90, and 158 mg/kg TMCP, respectively) for 13 weeks showed body weight gain decreases at the 3 highest feeding levels. All 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.[6] In a similar study in which rats were given oral doses by gavage of 50, 100, 200, 400, and 800 mg/kg for 13 weeks (equivalent to 10, 21, 42, 84, and 170 mg/kg TMCP, respectively), body weights at 200 mg/kg or higher 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.[6] In a similar pair of mouse studies, feeding of 250, 500, 1,000, 2,100, and 4,200 ppm (equivalent to about 10, 21, 42, 84, and 210 mg/kg TMCP, respectively) for 13 weeks produced cytoplasmic vacuolation in the adrenal glands in all groups. Hyperplasia of the gall bladder was found 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.[6] In the oral dosing portion, mice were given doses of 50, 100, 200, 400, or 800 mg/kg for 13 weeks (equivalent TMCP doses were 10, 21, 42, 84, and 168 mg/kg). Body weights of mice receiving 200 mg/kg or higher were reduced. Vacuolation of the adrenal glands was seen in all groups with 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 from 200 mg/kg and up was significantly reduced.[6]

Rats fed a mixture containing 60% to 65% TMCP for 3 months at doses of 30, 100, 300, and 1000 mg/kg showed no changes in tissues or organs upon histopathologic examination.[7] No immunotoxic effects were seen in mice given oral doses of 50 mg/kg once a week for 13 weeks.[14]

Chronic/Carcinogenic

A preparation of TCP containing 21% of the meta-isomer was tested in a 2-year feeding study. Rats were fed dietary levels of 75, 150, 300, or 600 ppm (equivalent to daily TMCP doses of about 0.8, 1.7, 3.2, and 5.2 mg/kg, respectively). Rats at 600 ppm were fed for 22 weeks then received control food for the duration of the study. Body weights, clinical observations, and survival of treated rats were similar to that of the controls. There were no chemically related increased incidences of neoplasms. 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, but not fed 600 ppm, for 22 weeks and allowed recovery to 2 years.[6] In a 2-year feeding study, mice were fed dietary levels of 60, 125, or 250 ppm (equivalent to daily TMCP doses of about 1.5,

3, and 6 mg/kg, respectively). Body weights, clinical observations, and survival of treated mice were similar to that of the controls. There were no chemically related increased incidences of neoplasms. 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.[6]

Genotoxic

A pure sample of TMCP was not mutagenic in 5 strains of *Salmonella typhimurium* when tested both with and without metabolic activation.[15] Using a preparation of TCP containing 21% of the meta-isomer, TMCP was not mutagenic in *Salmonella typhimurium* strains TA98, TA100, TA1535, or TA1537. It did not induce chromosomal aberrations or sister-chromatid exchanges in cultures of Chinese hamster ovary cells. These tests were conducted both with and without S9 metabolic activation.[6]

Reproductive and Developmental Toxicity

A mixture of TCP isomers (containing less than 9% TOCP, the remainder being a mixture of TCP and TMCP [with the TMCP content being unspecified, but a major 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 pups was reduced in both low- and high-dose groups along with decreased litter size and pup viability. Pup weights, structure, and developmental landmarks were unaltered. On histopathologic examination, both male and female reproductive organs showed damage .[16] Again using a mixture of TCP isomers (74.9% pure or mixed isomers with <0.1% pure triorthocresyl, 20.6% pure metacresyl, and 3.9% pure paracresyl phosphate) in a continuous breeding study, mice received dietary levels of 500, 1,000, or 2,000 ppm over 98 days. The fertility indices were not changed, but the number of females delivering live young pups 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

Single oral doses of 2, 20, or 200 mg/kg were given orally to rats and a single intravenous dose of 20 mg/kg was given and was well absorbed. TMCP was excreted primarily in the feces at all 4 dose levels and as the dose increased, the percentage excreted in the feces also increased, while that found in the urine decreased. Approximately 40% to 60% of the dose was excreted in the bile within the first 6 hours and the percentage appearing in the feces was less than that excreted in the bile, suggesting substantial enterohepatic recycling. Within 3 days, essentially all of the chemical was excreted. TMCP was rapidly distributed to the muscle and liver then redistributed to the adipose tissue and skin. There was no tendency of TMCP to bioaccumulate in specific organs or tissues. Although dermal absorption of this isomer was not evaluated, a single dermal application of TOCP was well absorbed and the similarity of structure and physical properties make it likely that the meta-isomer will be well absorbed through the skin.[6] However, a single dermal dose of 500 mg/kg of TMCP administered to rabbits resulted in 92% eliminated in the feces within 4 days.[18]

TLV Chronology

Table 2. TLV Chronology: *Trimetacresyl 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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