TEPP

CAS number: 107-49-3

Synonyms: Ethyl pyrophosphate, phosphoric acid tetraethyl ester, tetraethyl pyrophosphate, Bladan®, Fosnex®, HETP®, Nifos T®, Kilmite®, Pyfos®, Tetraspa®

Chemical formula: $C_8H_{20}O_7P_2$

Workplace exposure standard (amended)

TWA: —

STEL: —

Peak limitation: —

Notations: **Sk.**

IDLH: **5 mg/m^3**

Sampling and analysis: N/A

Recommendation and basis for workplace exposure standard

This chemical has been nominated for removal from the *Workplace exposure standards for airborne contaminants* due to a lack of evidence that it is used or generated in Australian workplaces or that it presents a potential for legacy exposure. Therefore, a TWA is not recommended.

Discussion and conclusions

Tetraethyl pyrophosphate (TEPP) is an organophosphorus (OP) pesticide used to control aphids, spiders, mites and other insects. There is lack of evidence that this chemical is used or generated in Australian workplaces or that it presents a potential for legacy exposure.

Critical effects of exposure are a reduction in ChE enzymes in red blood cells (RBC), plasma and the brain.

No data in humans involving workplace exposure to airborne concentrations are available. It is a potent, rapid-acting OP reported to produce signs of cholinergic toxicity including death from accidental and intentional poisoning in humans. A steep dose-response curve producing signs of cholinergic response in humans is reported in clinical reports of therapeutic use. The difference between the dose required to produce a response and the dose that produced toxicity was extremely small (ranging from 0.07–0.4 mg/kg/d) in a therapeutic study of patients treated with daily doses between 13 and 17 mg/day. Intramuscular dosing in therapeutic use is reported to be four times more effective than oral dosing (ACGIH, 2018). A TLV-TWA of 0.01 mg/m^3 by ACGIH, 2018 is extrapolated from intramuscular dose used in a therapeutic trial. While MAK of 0.06 mg/m^3 by DFG, 2002 is based on analogy with other OP pesticides.

This chemical has been nominated for removal from the WES list. A TWA is not recommended.

Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended based on evidence of systemic effects in humans following dermal exposure.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 0.004 ppm (0.047 mg/m^3)***
ACGIH	***2007***	***TLV-TWA: 0.0008 ppm (0.01 mg/m^3)***

TWA-TLV recommended to protect against cholinergic and other adverse biologic effects

Summary of data:

Basis for TLV:

- Potent, rapid-acting OP with high toxicity; reports of signs of cholinergic response including death in humans.
- Quantitative data associated with the clinical reports on its therapeutic use to treat glaucoma and myasthenia gravis is the basis of the TLV-TWA
- Intraocular instillation doses between 0.01–0.4 mg/kg caused miosis (a positive cholinergic sign of response). A steep dose–response curve is reported with a dose of 0.01 mg/kg reversible in 30 min and a dose of 0.1 mg/kg reversible in 3 wk. A NOAEL for clinical effects is not clear from the available data and no further information of the reversibility of effects is provided
- Intramuscular dosing 4 times as effective as oral dosing. An intramuscular dose of 0.007 mg/kg caused a 25% reduction in RBC ChE activity ≡oral dose 0.03 mg/kg (no further information provided)
- Given that inhibition of RBC ChE appears to be the first sign of response, a 25% reduction is considered of marginal significance. Therefore, a dose of 0.003 mg/kg (order of magnitude less) unlikely to produce significant enzyme inhibition
- An oral dose of 0.003 mg/kg ≡inhalation exposure of 0.02 mg/m^3 (assuming 70 kg worker and 10 m^3 inhaled per 8 h workday). However, based on the steep dose-response curve and quality of the database, a lower value is warranted. Therefore, a TLV-TWA of 0.01 mg/m^3 is recommended. TLV–TWA is sufficiently low to be protective of short-term exposure peaks; no TLV-STEL recommended
- Both particulate mass and vapor phase concentrations should be considered in determining total airborne concentration.

Human data:

- Serious poisoning within 1 h reported in case of accidental poisoning where a crop-dusting pilot spilled TEPP concentrate directly on his leg:
  - blurred vision, weakness and light-headedness, followed by vomiting, unconsciousness, cyanosis and frothing of foamy material from the nose and mouth
  - successfully treated at a hospital and released 50 h later
  - other cases reported death following accidental spilling on the skin
- Accidental and intentional contact is reported to result in deaths based on following reports by 1959:
  - 8 poisonings during spraying
  - 18 by other accidents
  - 101 suicide attempts (of which 99 deaths reported)
  - One mouthful reported to result in complete collapse in less than 5 min followed by death

Source	Year set	Standard

• Used to treat glaucomatous eyes since it reduces intraocular tension
• One drop of a 0.01% solution produced miosis in 30 min that lasted for a day:
  ○ 0.1% solution produced miosis at 7 min and lasted 3 wk
• In another study using two-drop doses of 0.1% (≈0.3 mg/kg) within 30 min:
  ○ mild headache, sensation of pressure in the eyeball and burning of the lids reported
• Results of a study to evaluate its use in treatment for myasthenia gravis; oral, intramuscular (IM), intravenous (IV) or intra-arterial injections of 18 normal human subjects:
  ○ IM or IV administration of ~0.0143 mg/kg caused rapid reduction of plasma ChE and RBC AChE (60% of control)
  ○ ≈4 times larger oral doses were required to produce a similar effect; no further details
  ○ IM dose of 0.007 mg/kg reduced plasma ChE 80% and RBC AChE 25%;
  ○ using the effective oral dose of 4 x that of the IM dose i.e. oral dose of 0.03 mg/kg is expected to lower RBC ChE by 25%
• Results of a study for myasthenia gravis treatment (daily dose between 13–17 mg/d) indicated a steep dose-response curve:
  ○ difference between a dose required to produce a maximal response and a dose that produced toxicity was small, ranging from 0.5–3.0 mg (0.07–0.4 mg/kg).
Animal data:
• Dermal LD_{50}: 2.4 mg/kg (male rats); 1.2 mg/kg (rabbits)
• 1 h LC_{50}: 23.5 mg/m^3 and a 4-h LC_{50}: 6.75 mg/m^3 (male rats)
• No further studies identified.		

DFG	***2002***	***MAK: 0.005 ppm (0.06 mg/m^3)***
MAK first established in 1958 then reviewed 1973 and 2002 with no change. Summary of additional information: • MAK derived by analogy with other OP pesticides; no further information • No data for humans from which a conclusion can be drawn in the case of measured workplace concentrations and effects on ChE; no further information provided.		
SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***NA***	***NA***
No report.		

Secondary source reports relied upon

NIL.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?	Insufficient data
Is the chemical carcinogenic with a mutagenic mechanism of action?	Insufficient data

Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	Skin
HCIS	—
NICNAS	NA
EU Annex	NA
ECHA	—
ACGIH	Skin
DFG	H(skin)
SCOEL	NA
HCOTN	NA
IARC	NA
US NIOSH	SK:SYS

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

Skin notation assessment

Calculation	
Adverse effects in human case study:	yes
Dermal LD_{50} ≤1000 mg/kg:	yes
Dermal repeat-dose NOAEL ≤200 mg/kg:	
Dermal LD_{50}/Inhalation LD_{50} <10:	
In vivo dermal absorption rate >10%:	
Estimated dermal exposure at WES >10%:	
	a skin notation is warranted

IDLH

Is there a suitable IDLH value available?	Yes

Additional information

Molecular weight:	290.19
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 11.87 mg/m^3; 1 mg/m^3 = 0.08 ppm
This chemical is used as a pesticide:	☐
This chemical is a biological product:	☐
This chemical is a by-product of a process:	☐
A biological exposure index has been recommended by these agencies:	✓ ACGIH ☐ DFG ☐ SCOEL

Workplace exposure standard history

Year	Standard
Click here to enter year	

References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the *TLVs® and BEIs® Guidelines section* on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2002) TEPP (O,O,O,O-Tetraethylpyro- phosphat) – MAK value documentation.

European Chemicals Agency (ECHA) (2019) TEPP (ISO); tetraethyl pyrophosphate – REACH assessment.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – TEPP.

US National Institute for Occupational Safety and Health (NIOSH) (2015) NIOSH Skin Notation Profiles: Tetraethyl pyrophosphate (TEPP).