TRIMETHYL PHOSPHITE

CAS number: 121-45-9

Synonyms: Methyl phosphite, phosphorus acid trimethyl ester, TMP, trimethoxyphosphine

Chemical formula: $C_3H_9O_3P$

Workplace exposure standard (retained)

TWA: **2 ppm (10 mg/m^3)**

STEL: **—**

Peak limitation: **—**

Notations: **—**

IDLH: **—**

Sampling and analysis: The recommended value is quantifiable through available sampling and analysis techniques.

Recommendation and basis for workplace exposure standard

A TWA of 2 ppm (10 mg/m^3) is recommended to protect for irritation of the eyes, skin and respiratory tract in exposed workers.

Discussion and conclusions

Trimethyl phosphite (TMP) is used as an intermediate in the manufacture of pesticides and flame-retardant polymers and as a fireproofing agent in the production of textiles.

The critical effects of exposure are irritation of the eyes, skin and respiratory tract.

Limited human data are available. Workers at a manufacturing plant exposed at average concentrations between 0.3 and 4 ppm and occasionally up to 15 ppm, did not experience eye or other adverse effects (ACGIH, 2018). A threshold of 20 ppm is reported for significant nuisance odour in workers (ACGIH, 2018; DFG, 1984). Irritation of the eyes occurs at 50 ppm or higher during sub-chronic inhalation studies in rats, with respiratory distress, reduced body weight gain and lung inflammation occurring at approximately 500 ppm and greater. A NOAEC of 10 ppm is reported from these studies (ACGIH, 2018; NICNAS, 2016).

A TWA of 2 ppm (10 mg/m^3) is recommended to be retained based on the NOAEC of 10 ppm in animals and is considered protective of irritant effects.

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.

There are insufficient data to recommend a skin notation.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 2 ppm (10 mg/m^3)***
ACGIH	***2001***	***TLV-TWA: 2 ppm (10 mg/m^3)***

TLV-TWA recommended to minimise the potential for ocular and skin irritation.

Summary of data:

No specific derivation provided; based on ocular effects observed in rats exposed at >10 ppm, therefore TLV should not exceed this concentration. In addition, no significant adverse effects in workers exposed at 1 ppm.

Human data:

- At manufacturing plant odour not considered objectionable by workers until concentrations approached 20 ppm
- Average concentrations between 0.3 and 4 ppm and occasional values up to 15 ppm, reported in studies of workplace air in manufacturing plant (in 1979):
  - no indications of ocular or other adverse effects in 179 employees

Animal data:

- LD_{50}: 2,500– 2,890 mg/kg (rats, oral)
- LD_{50}: 2,600 mg/kg (rabbits, dermal); no signs of ChE inhibition
- Moderately severe and persistent irritation to rabbit skin (topical application)
- Severe ocular irritation and swelling (lasting several days) following instillation (undiluted) to rabbit eye
- LC_{50}: >10,000 ppm (rats, inhalation, 4 h); profound discomfort, irritation and respiratory distress
- 8 wk study in rats exposed at 500±75 ppm for 7.5 h/d, 5 d/wk caused respiratory distress, reduced body weight gain
- Exposures at 100 ppm, 300 ppm and 600 ppm in rats, 6 h/d, 5 d/wk, 4 wk duration:
  - >70% mortality at 600 ppm and 10% mortality at 300 ppm
  - evidence of lung inflammation at 600 ppm
  - ocular irritation at 100 ppm or higher
  - severe cataracts developed in 600 ppm exposure group; mild cataracts at 300 ppm; mild, reversible striate opacities of lenses of a few animals in 100 ppm exposure group.
- Exposures at 10 ppm, 50 ppm and 100 ppm in rats (duration and rate not provided):
  - superficial irritation of cornea at 50 and 100 ppm with mild cataracts in females only
  - no effects in 10 ppm exposure group.
- Pregnant rats given 16, 49 or 164 mg/kg/d by oral gavage on GD 6–15:
  - increased number of litters with gross abnormalities in 164 mg/kg/d group
  - no changes in offspring of lower dose groups.
- Genotoxic in 3 separate mouse lymphoma assays; positive in *D melanogaster* mutagenicity assays and bacterial damage/repair suspension assay using various strains of *E coli* and *S typhimurium*
- Negative results in cell transformation assay, bacterial DNA repair assay, 2 *Salmonella*/ mammalian-microsome pre-incubation assays or *Salmonella* and *Saccharomyces* strains.

Source	Year set	Standard
Insufficient data available to recommend, skin, SEN or carcinogenicity notations or TLV-STEL.		
DFG	***1984***	***Not assigned***

Summary of additional data:
• Laboratory study with test subjects determined odour threshold of 0.0001 ppm:
  ○ smell at the workplace below 20 ppm should not be considered a nuisance
• Main symptoms in animals following long-term inhalation 'at high concentrations' are irritation to eyes, outer skin and lungs
• In undiluted or vapour form can cause strong but reversible irritation, swelling and lens clouding of the eye, lasting several days
• Inhalation study in rats cited in ACGIH (2001) with exposures at 0, 10, 50 and 100 ppm conducted for 4 wk, exposed for 6 h/d, 5 d/wk
• 90 d gavage study in rats, dosed at 0, 40, 80 or 160 mg/kg; the following effects occurred at 160 mg/kg/d only:
  ○ 7/30 rats died
  ○ weight loss in males and females
  ○ red discolouration of lung parenchyma
  ○ histopathologic changes in testes and liver; reduced sperm production in 11/12 males
• 21 d dermal study in rabbits caused mild (0.3 g/kg), marked (0.6 g/kg) or severe erythema (1.2 g/kg):
  ○ all animals showed reduced movement activity immediately following application and highest dose group lost righting reflex
• Carcinogenicity studies not published to date.
 	
While 20 ppm is considered a threshold value (for significant odour nuisance) based on field experience, data from longer exposures at or below this value and a definite NOEC is lacking, therefore MAK not assigned. Further testing on teratogenic effects, mutagenicity and carcinogenic potential also required.		

SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***NA***	***NA***
No report.		

Secondary source reports relied upon

Source		Year	Additional information
NICNAS	✓	2016	• Due to range in dermal LD_{50} data, not possible to draw conclusion on chemicals' acute dermal toxicity • Low acute inhalation toxicity

Source	Year	Additional information
		• Irritation to eyes, skin and upper respiratory system reported in humans; no further information • Not considered to cause severe health effects from repeated oral exposure, except at doses >160 mg/kg/d • NOAELs of 33 to 80 mg/k/d from 21 to 90 d gavage study in rats • NOAEC of 10 ppm; whole body exposure; inhalation studies cited in ACGIH (2001) • May be mutagenic in germs cells: ○ data inconclusive due to lack of *in vivo* studies.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic? Insufficient data

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

Notations

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

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:	
Dermal LD_{50} ≤1000 mg/kg:	no
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 not warranted

IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	124.08
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 5.07 mg/m^3; 1 mg/m^3 = 0.197 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) (1984) Trimethylphosphit – MAK value documentation.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) Phosphorous acid, trimethyl ester: Human health tier II assessment – IMAP report.