FENAMIPHOS

CAS number:	22224-92-6
Synonyms:	ENT 27572, ethyl 3-methyl-4-(methylthio)phenyl(1-methylethyl)-phosphoramidate, nemacur
Chemical formula:	$C_{13}H_{22}NO_3PS$
Structural formula:	—

Workplace exposure standard (amended)

TWA:	**0.05 mg/m^3 (inhalable fraction and vapour)**
STEL:	**—**
Peak limitation:	**—**
Notations:	**Sk.**
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 0.05 mg/m^3 is recommended to protect for cholinergic effects in exposed workers.

Discussion and conclusions

Fenamiphos is an organophosphate insecticide that is no longer registered for use in Australia. Based on animal studies, the critical effect of exposure is cholinesterase inhibition. Acute toxicity in humans has been associated with nausea, vomiting and abdominal pain (ACGIH, 2018)

Human exposure data are limited and the recommended TWA is based on chronic and sub-chronic feeding studies in dogs and rats (ACGIH, 2018). Dogs are considered the sensitive species and NOAELs for red blood cell (RBC), plasma and brain cholinesterase inhibition range from 0.025 to 0.04 mg/kg/day.

It is recommended that the TWA of 0.05 mg/m^3 derived by ACGIH (2018) be adopted. ACHIH derived the TWA by calculating an equivalent inhalational NOAEC based on the NOAEL of 0.025 mg/kg/day in the dog study reported by ACGIH (2018). Results of a three-week inhalational study in rats support the extrapolation from oral studies. The recommended TWA is considered to protect for cholinesterase inhibition in exposed workers.

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 for dermal absorption and adverse systemic effects in animals.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 0.1 mg/m^3***
ACGIH	***2006***	***TLV-TWA: 0.004 ppm (0.05 mg/m^3) inhalable fraction and vapour***

TLV-TWA intended to protect for cholinergic effects reported in animal studies. Insufficient data to recommend a TLV-STEL.

Summary of data:

TLV-TWA derived from NOAELs between 0.025–0.04 mg/kg/d for cholinesterase inhibition in dogs from chronic and sub-chronic feeding studies. Dogs were the most susceptible tested species, rats generally exhibited slightly higher NOAELs. The equivalent air concentration exposure to the NOAEL of 0.025 mg/kg/d was calculated to be 0.18mg/m^3 assuming 100% absorption in a 70-kg person with a respiratory volume of 10 m^3 during an 8-h shift. The TWA is intended to be measured as the combined inhalable particulate fraction and vapour to account for potential evaporative losses during sampling, hence a factor of 2 is applied to account for translation from experimental conditions to the workplace and a factor of 1.4 is applied to account for allometric conversion to human exposure. The TLV-TWA of 0.05 mg/m^3 is therefore considered sufficiently protective of cholinergic effects in workers.

Human data:

- Accidental exposure associated with nausea, vomiting and abdominal pain
- Workers handling the substance for an agricultural application were exposed to <0.001 mg/h by inhalation and 93–667 µg/h by dermal absorption (no further details; no details on adverse effects).

Animal data:

- Slightly irritating to skin and eyes (rabbits); non-sensitising to skin (guinea pigs)
- Oral LD_{50}: 2.7–19.4 mg/kg (rats); 75–100 mg/kg (guinea pigs); 5–17.5 mg/kg (rabbits)
- Dermal LD_{50}: 72–154 mg/kg (rats); 178–225 mg/kg (rabbits):
  - brain and RBC cholinesterase inhibition at 2.5–10 mg/kg/d (rabbits, dermal repeat dose, 21 d)
- LC_{50}: 110–175 mg/m^3 (1 h); 91–100 mg/m^3 (unspecified species, 4 h):
  - cumulative effect observed after 5 consecutive doses: LC_{50} between 28–100 mg/m^3 (unspecified species, 4 h/d, 5 d)
- Chronic feeding study with diet containing 0, 0.5, 1, 2, 5 or 10 ppm (equivalent to 0, 0.01, 0.025, 0.05, 0.125 and 0.250 mg/kg/d) (dogs, 2 yr):
  - no cholinergic signs or other signs of toxicity in any group
  - plasma and RBC cholinesterase activities inhibited at 2 ppm (0.05 mg/kg/d)
  - NOEL of 1 ppm (0.025 mg/kg/d) for plasma and RBC cholinesterase inhibition
- Sub-chronic feeding study with diet containing 0, 0.6, 1.0 or 1.7 ppm (equivalent to 0.02, 0.03 or 0.04 mg/kg/d) (dogs, 100 days):
  - no effect on plasma cholinesterase in females and RBC and brain cholinesterase in both sexes in any group
  - NOEL of 1.7 ppm (0.04 mg/kg/d)
- Repeat inhalation study with treatment range 0.03–3.5 mg/m^3 (rats, 6 h/d, 5 d/wk, 3 wk):
  - NOAEL: 0.25 mg/m^3 and LOAEL: 3.5 mg/m^3 for plasma cholinesterase inhibition, supports NOAEC extrapolated from feeding studies

Source	Year set	Standard
• Equivocal evidence for induction of chromosomal aberration *in vitro*, otherwise non-mutagenic • Multigenerational reproductive studies indicate foetal toxicity (reduced bw gain) occurs at maternally toxic concentrations >0.15 mg/kg/d (rats, 2–3 generation studies); neonates fed 10 ppm of diet exhibited similar RBC cholinesterase inhibition to adults. Negative carcinogenicity in chronic animal exposure studies supports an A4 classification. A skin notation is assigned due to lethality reported in dermal application studies with animals. Negative skin sensitisation results in animals do not warrant a dermal sensitiser notation.		
DFG	***NA***	***NA***
No report.		
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	✓		• Tier I assessment: agricultural and therapeutic uses are excluded from assessment.

US EPA	✓	1987	• Chain-fused sternebrae reported in developmental study at 0.3 mg/kg/d (rabbits); effects occurred above maternally toxic levels:
			  ○ maternal NOAEL: 0.1 mg/kg/d, LOAEL: 0.3 mg/kg/d
			  ○ foetal NOAEL: 0.3 mg/kg/d, LOAEL; 1 mg/kg/d
			• Inhalational reference dose not yet established
			• Assessment of carcinogenic potential in human not complete.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?	Insufficient data
Is the chemical carcinogenic with a mutagenic mechanism of action?	No

The chemical is not a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	Skin
HCIS	—

Source	Notations
NICNAS	NA
EU Annex	—
ECHA	—
ACGIH	Carcinogenicity – A4, Skin
DFG	NA
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:	yes
Dermal repeat-dose NOAEL ≤200 mg/kg:	yes
Dermal LD_{50}/Inhalation LD_{50} <10:	
In vivo dermal absorption rate >10%:	
Estimated dermal exposure at WES >10%:	
	consider assigning a skin notation

IDLH

Is there a suitable IDLH value available? No

Additional information

Molecular weight:	303.4
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 12.4 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.

European Chemicals Agency (ECHA) (2019) Fenamiphos – REACH assessment.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2018) Phosphoramidic acid, (1-methylethyl)-, ethyl 3-methyl-4-(methylthio)phenyl ester: Human health tier I assessment – IMAP report.

Tenth Adaptation to Technical Progress Commission Regulation (EU Annex) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).

US Environmental Protection Authority (US EPA) (1987) Integrated Risk Information System (IRIS) Chemical Assessment Summary – Fenamiphos.