THIRAM

CAS number: 137-26-8

Synonyms: bis(Dimethylthio carbamoyl) disulphide, tetramethylthioram disulphide, tetramethyl thioperoxydicarbonic diamide, TMT, TMTD, TMTDS

Chemical formula: $C_6H_{12}N_2S_4$

Workplace exposure standard (retained)

TWA: **1 mg/m^3**

STEL: **—**

Peak limitation: **—**

Notations: **Sk., DSEN, RSEN**

IDLH: **100 mg/m^3**

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

Recommendation and basis for workplace exposure standard

A TWA of 1 mg/m^3 is recommended to protect for adverse haematological effects in exposed workers.

Given the limited data on potential irritational endpoints available from the primary sources, it is recommended that a review of additional sources be conducted at the next scheduled review.

Discussion and conclusions

Thiram is used as a fungicide, rubber vulcaniser and bacteriostat in soap.

Critical effects of exposure are adverse haematological changes, irritation of the skin, mucous membranes and respiratory tract and dermal sensitisation.

Quantitative human exposure data are limited to clinical studies of dermal sensitisation in exposed workers that demonstrated dermal sensitisation potential. Haematological changes, including decreased red blood cell (RBC) count and haemoglobin (Hb) concentrations, are indicated as the most sensitive systemic endpoints in sub-chronic and chronic animal exposure studies with a NOAEL of 0.4 mg/kg/day in dogs and 0.5 mg/kg/day in rats (ACGIH, 2018; DFG, 2012; HCOTN, 2003). Thresholds for irritational endpoints and repeat inhalation studies are not documented in the available database. There is some evidence of mutagenicity. However, Thiram is not considered carcinogenic.

In the absence of quantitative inhalation data for humans or animals, the recommended TWA is based on sub-chronic and chronic oral studies with animals. The NOAEL for haematological changes ranges from 0.4 mg/kg/day in dogs to 3 mg/kg/day in mice and is equivalent to a NOAEC range of 2.8 to 4.2 mg/m^3. The TWA of 1 mg/m^3 by DFG (2012) is recommended to be retained and is considered sufficiently low to be protective of haematological changes. From the available source material, a threshold for irritation is unclear and should be sought from additional sources during next subsequent review.

Recommendation for notations

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

Classified as a skin sensitiser and a respiratory sensitiser according to the GHS.

A skin notation is recommended as evidence indicates allergic dermatitis in humans and animals.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 1 mg/m^3***
ACGIH	***2014***	***TLV-TWA: 0.005 ppm (0.05 mg/m^3) (Inhalable fraction and vapor)***

TLV-TWA intended to protect for irritation and dermal sensitisation.

Positive mutagenic potential is not associated with a carcinogenic mechanism of action; no evidence of carcinogenicity in chronic animal feeding studies, therefore not classified as a human carcinogen (A4).

Skin notation not recommended based on acute dermal application studies.

DSEN notation warranted based on reports of dermal sensitisation in humans and animals.

Summary of information:

In the absence of adequate human exposure data, TLV-TWA based on NOAEL of ≈0.5 mg/kg/d reported in sub-chronic and chronic feeding studies in rats and dogs. Equivalent inhalational dose calculated as 3.5 mg/m^3 assuming 100% absorption in a 70 kg worker with a respiratory volume of 10 m^3 during an 8 h shift. TLV-TWA of 0.05 mg/m^3 considered sufficiently low; however, derivation of the 70-fold UF is not presented or discussed by ACGIH.

Human data:

- Increased incidence of coughing, eye irritation, thoracic pain, tachycardia, dermal lesions and liver dysfunction in production workers (n=223). No further details
- Intolerance to alcohol manifested as flushing in face, rapid pulse, dizziness and hypotension presumably due to inhibition of acetaldehyde metabolism (no further details).

Animal data:

- LC_{50}: 300–1,000 mg/m^3 (rats, 4 h); rapid breathing, tremor and convulsions observed
- Dermal sensitisation reported in acute dermal application study (rabbits, no further details)
- NOAEL: 2.5 mg/kg/d for decreased food intake and changes in blood biochemistry in sub-chronic feeding study with dose groups 0, 2.5, 25 and 50 mg/kg/d (rats, 13 wk)
- LOAEL: 2 mg/kg/d for blood biochemistry and haematological changes (decreased RBC and Hb concentration) in sub-chronic feeding study with dose groups 0, 2, 7 and 12 mg/kg/d (dogs, 13 wk):
  - no histopathologic changes observed in any groups
- NOAEL: 0.5 mg/kg/d for haematological changes and decreased body and relative organ weight (heart, liver, kidney, spleen) in chronic feeding study with dose groups 0, 0.05, 0.5, 5, 50 mg/kg/d (rats, 2 yr):
  - no increased incidence of tumours in any groups
  - stomach irritation and inflammation observed in all groups
  - plasma carboxylesterase inhibition at 5 and 50 mg/kg/d
  - agency considers LOAEL of 0.05 mg/kg/d inconsistent with results of other chronic feeding studies and therefore uses NOAEL of 0.5 mg/kg/d for haematological endpoints as point of departure
- NOAEL: 1–1.5 mg/kg/d for haematological changes and carcinogenicity in 2 separate chronic feeding studies with dose range 0–15 mg/kg/d (rats, 2 yr)

Source	Year set	Standard
• NOAEL: 0.4 mg/kg/d for nausea, vomiting, fundal haemorrhage, miosis, liver and kidney damage and haematological changes in chronic gavage capsule study with dose groups 0, 0.4, 4 and 40 mg/kg/d (dogs, 2 yr) • Equivocal evidence for mutagenicity *in vitro* in bacteria, positive mutagenicity *in vitro* in human lymphocytes and testicular cells, positive sex-linked recessive lethal assay *in vivo* with *Drosophila melanogaster.* Insufficient data to recommend a TLV-STEL or RSEN notation.		
DFG	***2007***	***MAK: 1 mg/m³***
Summary of additional information: In the absence of adequate inhalational data for humans or animals, MAK derived from NOAEL of 3 separate chronic oral dose studies with rats, mice and dogs (also cited by ACGIH, 2018). The NOAEL in these species ranged from 0.4–3 mg/kg/d, converted to an equivalent inhalational NOAEC of 2.8–4.2 mg/m³ assuming 100% absorption in a 70 kg worker with a respiratory volume of 10 m³ during an 8 h shift; additional factors of 7/5 to account for continuous exposure and species-specific allometric scaling factors applied to calculate NOAEC. Due to similarity in NOAEC estimates across species, humans not expected to be significantly more sensitive; MAK of 1 mg/m³ therefore expected to be protective. Not classified as a carcinogen based on overall negative mutagenicity of pure substance and lack of tumorigenicity in chronic animal feeding studies. Acute dermal toxicity is low, skin notation therefore not warranted. Dermal sensitisation evidenced in several clinical studies and controlled animal studies, warrants a dermal sensitiser (Sh) notation. Human data: • Positive dermal sensitisation evidenced in several clinical dermal sensitisation studies of rubber components testing pure thiram and mixtures: o positive dermal sensitisation in 1–2% of subjects (n=6,942) using 1% topical ointment in petrolatum. Animal data: • Non-irritating to rabbit skin after 4 h, slight irritation at 24 h (no further details provided): o irritating to eyes, reversible within 15 d (no further details provided) • NOAEL: 1.2/1.4 mg/kg/d (males/females) for reduced body weight, anaemia and muscular atrophy (females) in chronic feeding study with dose groups 0/0, 0.1/0.1, 1.2/1.4, 11.6/13.8 mg/kg/d (rats, 2 yr) • NOAEL: 3 mg/kg/d for skin inflammation and necrosis and decreased body weight in chronic feeding study with dose groups 0/0, 3/3, 24/57, 50/112 mg/kg/d (males/females) (mice, 2 yr) • Agency concludes pure substance is non-mutagenic based on results of several *in vitro* and *in vivo* assays. Insufficient data to recommend a respiratory sensitiser notation.		
SCOEL	***NA***	***NA***
No report.		

Source	Year set	Standard
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***2003***	***TWA: 5 mg/m^3***
Summary of additional information: Existing administrative OEL considered too high, HBROEL derived from NOAEL of 0.4 mg/kg/d in chronic feeding study in dogs (also cited by ACGIH, 2018 and DFG, 2012). Conversion to an inhalational equivalent in humans, application of an allometric scaling factor and overall UF of 9 to account for inter- and intraspecies differences affords an HBROEL of 0.2 mg/m^3 as a TWA. Available evidence does not warrant a skin notation. Human data: • Excessive exposure causes skin, mucous membrane and respiratory tract irritation, erythema, urticaria and conjunctivitis (no further details provided) • Reports of allergic dermatitis in rubber factory workers, users of thiram-containing soap, fungicide sprayers and from wearing rubber gloves. Animal data: • Gene mutations induced in sensitive strains of *S. typhimurium* and *E. coli* and mammalian cells at cytotoxic concentrations; no significant increase in micronuclei *in vivo* in mice, clastogenic effects only observed at maximum tolerated doses *in vivo.*		

Secondary source reports relied upon

Source		Year	Additional information
NICNAS	✓	2016	• Evidence for mutagenicity *in vitro* and in somatic cells *in vivo* based on weight of evidence of available data: ○ germ cell mutagenicity assays were overall negative • Not considered carcinogenic based on available chronic feeding studies with rats (also presented by ACGIH, 2018; DFG, 2012; HCOTN, 2003) • Decreased brain weights and increased hyperactivity at 21-44 mg/kg/d during wk 8 and 13 in repeat oral dose study (rats, 90 d).
IARC	✓	1991	• Eye irritation, coughing, chest pain, tachycardia, nose-bleed, dermal lesions, non-inflammatory heart disease, liver dysfunction and weakness reported in exposed production workers (n=223) compared with non-exposed control cases (n=193) (no details on exposure): ○ 7 cases of enlarged thyroid glands and 1 case of malignant thyroid lesion reported in 105 workers ○ thyroid gland disorders reported at 7.6% in exposed cases compared with 1.04% in non-exposed cases • Available data are inadequate to classify carcinogenicity in humans or animals (Group 3).
ECHA	✓	2020	• No quantitative dose-response data available for local effects on skin and respiratory tract

Source		Year	Additional information
			• Most sensitive local endpoint is skin sensitisation. • NOAEL: 0.84 (males) and 2.54 mg/kg/d (females) for changes in clinical chemistry, including decreased total protein, increased cholesterol and increased liver weight in chronic feeding study (dogs, 1 yr); LOAEL: 2.61 (males) and 7.23 mg/kg/d (females) • Long-term inhalation DNEL based on NOAEL of 0.84 mg/kg/d in male dogs; starting point was corrected to 1.475 mg/m^3 using 10 m^3 respiratory volume during 8-h shift in a 70-kg worker: ○ overall UF of 12.5 applied to account for inter- and intraspecies differences to arrive at long-term inhalational worker DNEL of 0.118 mg/m^3.
US NIOSH	✓	1994	• IDLH based on acute inhalation toxicity data in animals.

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	Sen
HCIS	Skin sensitisation – category 1
NICNAS	Skin sensitisation – category 1
EU Annex	Skin sensitisation – category 1
ECHA	—
ACGIH	Carcinogenicity – A4, DSEN
DFG	Sh (dermal sensitiser)
SCOEL	NA
HCOTN	—
IARC	Carcinogenicity – Group 3
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:	yes
Dermal LD_{50} ≤1000 mg/kg:	
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:	240.4
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 9.9 mg/m^3; 1 mg/m^3 = 0.10 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) (2012) Thiram – MAK value documentation, German language edition.

Health Council of the Netherlands (HCOTN) (2003) Thiram. Health-based Reassessment of Administrative Occupational Exposure Limits. The Hague: Health Council of the Netherlands; publication no. 2000/15OSH/090.

European Chemicals Agency (ECHA) (2020) Thiram – REACH assessment.

International Agency for Research on Cancer (IARC) (1991) Volume 53, Occupational Exposures in Insecticide Application, and Some Pesticides. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) Thioperoxydicarbonic diamide ([(H2N)C(S)]2S2), tetramethyl-: Human health tier II assessment – IMAP report.

Tenth Adaptation to Technical Progress Commission Regulation (EU) 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 National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – thiram.