TETRAHYDROFURAN

CAS number: 109-99-9

Synonyms: Cyclotetramethylene oxide, diethylene oxide, 1,4-epoxybutane, furanidine, hydrofuran, oxycyclopentane, onlane, tetrahydrofurane, THF, tetramethylene oxide

Chemical formula: C_4H_8O

Workplace exposure standard (amended)

TWA: **50 ppm (147 mg/m^3)**

STEL: **—**

Peak limitation: **—**

Notations: **Sk.**

IDLH: **2,000 ppm (10% LEL)**

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

Recommendation and basis for workplace exposure standard

A TWA of 50 ppm is recommended to protect for irritation to respiratory tract and effects on the liver, kidney and central nervous system (CNS) in exposed workers.

The evidence does not support the recommendation of a STEL.

Discussion and conclusions

Tetrahydrofuran (THF) is a solvent for natural and synthetic polymers and resins and is used as a monomer for the manufacture of polytetramethyleneoxide. It is used in the manufacture of lacquers, glues, paint, dyes, ink, adhesives, PVC pipe cement and magnetic tape.

Critical effects of exposure are irritation to respiratory tract mucous membrane, nephropathy (kidney effects), liver cell proliferation and CNS effects. Case studies report complaints of nausea, dizziness, hypoacusis (partial loss of hearing), angioedema and occipital headache at high concentrations; and irritation to the skin, eyes and mucous membranes at unspecified concentrations (ACGIH, 2018).

No irritation of the respiratory tract reported after exposure for six minutes at 400 ppm and 15 minutes at 200 ppm in volunteers (DFG, 1996). Rats exposed at 100 to 200 ppm for three hours developed slight local irritation such as redness of the nose and eyelids (ACGIH, 2018). Slight damage to the nasal epithelium is observed after rats were exposed by inhalation at 100 ppm for three weeks (DFG, 1996). A NOAEC of 200 ppm, for nasal and ocular secretions is reported in a 13-week study in mice (NICNAS, 2013). A NOAEC of 200 ppm is determined for cell proliferation induction in the liver of female mice and in the kidney of male rats in a sub-chronic study (ACGIH, 2018). Carcinogenic effects are observed in rodents. However, the exposures leading to these effects are outside the range considered relevant for long term human exposure (ACGIH, 2018; NICNAS, 2016).

A TWA of 50 ppm is recommended based on the evidence of irritation and nasal damage in animals at 100 ppm and is also supported by the data in humans. The TWA of 50 ppm is consistent across ACGIH (2018), DFG (1996) and SCOEL (1992) sources. This TWA is expected to be protective of irritant effects, effects on the kidneys, liver and on the CNS based on the weight of evidence reported in the primary sources.

The data does not support the recommendation of STEL.

Recommendation for notations

Not classified as a carcinogen category 2 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 as evidence indicates rapid absorption through the skin and contribution to adverse systemic effects.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 100 ppm (295 mg/m^3)***
ACGIH	***2005***	***TLV-TWA: 50 ppm (147 mg/m^3); TLV-STEL: 100 ppm (295 mg/m^3)***

TLV-TWA recommended to protect against irritation to respiratory tract mucous membrane, nephropathy, liver cell proliferation and CNS effects.

TLV-STEL recommended to prevent acute irritation, neurotoxicity and CNS effects.

Summary of data:

TLV-TWA based on NOEC of 200 ppm for adverse effects identified in animal studies.
TLV-STEL based on animal studies suggesting the previous STEL of 250 ppm was too high to prevent acute neurotoxicity effects.

Human data:

- Reported to be irritating to the skin, eyes and mucous membranes although no specific concentration for irritation described
- Individuals exposed at high concentrations have elevated circulating liver enzymes and complained of nausea, dizziness, hypoacusis, angioedema and occipital headache; no further information
- A worker exposed over 2 wk at an unspecified concentration was hospitalised for unrelated condition:
  - following enflurane anaesthesia the patient developed cerebral convulsions/seizures
  - the authors of the case report suggested the interaction of the anaesthetic and occupational exposure to THF might have contributed to the convulsions
- Case study: neurobehavioural and prevalence of headache and irritation of the nose and eyes reported in 19 workers exposed to mixed solvent exposures of MEK (11–128 ppm), THF (7–22 ppm), toluene and cyclohexanone:
  - workers exposed to the solvent mixture had poorer visual motor control and recent memory impairment when compared to non-exposed. No further information
- No contact or sensitisation reactions noted other than defatting action in an undescribed dermatitis test on 196 people
- A cohort investigation of 14,067 workers was undertaken following concerns of oesophagus cancer in a plant:
  - a non-statistically significant increase in oesophageal cancer noted (standard mortality rate [SMR]=1.140)
- Dermal route of entry of vapour at 150 ppm for 4 h compared to combined inhalation and dermal routes of entry:
  - the dermal route alone, accounted up to 6% of the total body burden of both routes measured by post-exposure in blood, breath, and urine.

Animal data:

- LC_{50}: ~22,000 ppm (mice, 2 h)
- Rats exposed at 100–200 ppm for 3 h developed slight local irritant symptoms, such as redness of the nose and eyelids. No further information

Source	Year set	Standard

- Male rats and female mice received either a 4 h (rats) or a 2 h (mice) inhalation exposure in a study to identify acute neurotropic effects:
  - criteria involved the inhibition of propagation and maintenance of electrical-evoked seizure discharge
  - estimates of 10% and 30% depression from pre-exposure values were 290 and 1220 ppm in rats and 190 and 290 ppm in mice, respectively
  - authors concluded a STEL of 250 ppm did not protect exposed humans
- Rats and mice exposed by inhalation 6 h/d, 5 d/wk for 105 wk at 0, 200, 600, or 1,800 ppm:
  - incidence of nephropathy statistically significantly greater than the chamber controls at 200 ppm male mice
  - female mice exposed to the highest concentrations showed a significant increase in hepatocellular adenomas and carcinomas, either alone or combined
  - at 600 and 1,800 ppm concentrations, a non-statistically significant increased incidence of renal tubule epithelial adenomas and carcinomas combined (p=0.065 for 1800 ppm THF)
- A 20-d study was conducted to examine enzyme induction and cell proliferation (follow up to 105 wk study); female mice and male rats exposed by inhalation for 5 d/w for 4 wk at 0, 200, 600 and 1,800 ppm:
  - a NOEC of 200 ppm determined for cell proliferation induction in the liver of female mice and in the kidney of male rats
- The following results reported in rats and mice exposed 6 h/d, 5 d/wk for 14 wk at 0, 66, 200, 600, 1,800 or 5,000 ppm:
  - both male and female rats exhibited ataxia, lower thymus and spleen weights, and a higher incidence of hyperplasia at 5,000 ppm
  - female rats exhibited lower liver weights at 5,000 ppm
  - liver weights increased for male mice exposed at 600 ppm or greater
  - the NOEC for increased liver weights in male mice was 200 ppm
- A NOEC of 200 ppm determined for cell proliferation induction in the liver of female mice and in the kidney of male rats
- Rapidly absorbed through skin of rabbits and fatal to rats when 10% body surface exposed to the liquid
- Not mutagenic *in vitro* or *in vivo*.

Insufficient data to recommend a sensitiser notation.

DFG	***1996***	***MAK: 50 ppm (150 mg/m^3)***

MAK lowered to 50 ppm based on evidence of nasal epithelium damage of rats exposed at 100 ppm.

Summary of additional data:

- No irritation reported 15 min after the beginning of a 3 h exposure at 50 and 200 ppm, and 6 min after exposure to 400 ppm in volunteers. No further information
- Slight damage to the nasal epithelium observed after rats exposed by inhalation at 100 ppm for 4 h/d, 5 d/wk for 3 wk:
  - more marked morphological damage to the tracheal and nasal mucosa occurred at 5,000 ppm. No further information
  - basis for MAK
- Insufficient data available regarding dermal absorption:

Source	Year set	Standard
		○ very good dermal penetration is to be expected ○ after direct contact in workers, high concentration in urine noted 16 h post exposure ○ the short half-time, indicates a skin depot (no further information) • Taking into consideration the physicochemical properties designated with an “H” skin notation.
SCOEL	***1992***	***TWA: 50 ppm (120 mg/m³); STEL: 100 ppm (300 mg/m³)***
Summary of additional data: • TWA based on 3 wk study in rats as cited by DFG (1996); an UF of 2 applied to account for the transient nature of the minimal effects observed • No derivation of STEL provided only that it should be applied to limit short-term exposure to irritant levels.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***2012***	***NA***
Review of carcinogenicity and genotoxicity; the available data are insufficient to evaluate the carcinogenic properties of THF.		

Secondary source reports relied upon

Source		Year	Additional information
NICNAS	✓	2013	• No contact dermatitis or sensitisation observed in 196 volunteers exposed to the chemical dermally (exposure concentration not reported) • A NOAEC of 200 ppm, for nasal and ocular secretions (1/20) reported in 13 wk study in mice (study cited by ACGIH, 2018).
NICNAS	✓	2016	• *Clear evidence of carcinogenic activity* in female mice based on increased incidence of hepatocellular adenoma or carcinoma; *some evidence of carcinogenic activity* in male rats based on increased incidence of combined renal tubule neoplasms (either adenoma or carcinoma) (cited by ACGIH, 2018) • No genotoxicity *in vitro* and *in vivo* and causes carcinogenic activity only at high doses levels • Rodent carcinogenicity data considered relevant to humans: ○ exposures leading to these tumours are outside the range considered relevant for long term human exposure.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?	No

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

Notations

Source	Notations
SWA	Skin
HCIS	Carcinogenicity – category 2
NICNAS	—
EU Annex	NA
ECHA	NA
ACGIH	Carcinogenicity – A3, Skin
DFG	Carcinogenicity – 4, H (skin)
SCOEL	Skin
HCOTN	Carcinogenicity – category 3
IARC	Carcinogenicity – Group 2B
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
Insufficient data to assign a skin notation.

IDLH

Is there a suitable IDLH value available?	Yes, based on LEL

Additional information

Molecular weight:	72.11
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 2.95 mg/m^3; 1 mg/m^3 = 0.34 ppm
This chemical is used as a pesticide:	☐
This chemical is a biological product:	☐
This chemical is a by-product of a process:	☐

Molecular weight:	72.11
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 2.95 mg/m^3; 1 mg/m^3 = 0.34 ppm
This chemical is used as a pesticide:	☐
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.

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EU Scientific Committee on Occupational Exposure Limits (SCOEL) (1992) Recommendation from the Scientific Committee on Occupational Exposure Limits for Tetrahydrofuran. SCOEL/SUM/12C.

Health Council of the Netherlands (HCOTN) (2012) Tetrahydrofuran. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2012/23.

International Agency for Research on Cancer (IARC) (2019) Tetrahydrofuran. IARC Monographs on the evaluation of the carcinogenic risk to humans.

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National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) Furan, tetrahydro: Human health tier III assessment – IMAP report.

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