URETHANE

CAS number: 51-79-6

Synonyms: Carbamic acid, ethyl ester, leucothane, pracarbamin

Chemical formula: $C_3H_7NO_2$

Workplace exposure standard (new)

TWA: —

STEL: —

Peak limitation: —

Notations: **Carc. 1B, Sk.**

IDLH: —

Sampling and analysis: N/A

Recommendation and basis for workplace exposure standard

Insufficient data exist to perform a risk-based assessment and it is recommended that a review of additional sources be conducted at the next scheduled review.

Discussion and conclusions

Urethane is used as an intermediate in textile resins and pharmaceuticals and as a solubilising agent in the manufacture of pesticides and cosmetics. It is not used in the production of polyurethane foams and coatings, nor is it released upon their decomposition.

The critical effects of exposure are liver, heart and lung carcinogenicity as observed in rodents.

No quantitative human exposure data are available. The production of genotoxic metabolites by oxidative enzymes in rodents and humans is clearly evidenced *in vitro* (DFG, 2004; SCOEL, 2012). A genotoxic mechanism of carcinogenicity is supported by evidence of the formation of these metabolites *in vivo* in mice and increased incidence of liver, heart and lung cancers in several carcinogenicity studies with rodents using either the substance or its genotoxic derivatives (DFG, 2004; SCOEL, 2012). No epidemiological data are available to confirm carcinogenicity in humans. However, the metabolism to genotoxic carcinogens observed in rodents is expected to occur also in humans (IARC, 2010).

The available primary source evaluations uniformly do not recommend a numerical WES equivalent due to the non-threshold-based genotoxic carcinogenicity demonstrated in rodents, which is likely to occur in humans (DFG, 2004; HCOTN, 2000; SCOEL, 2012). In the absence of a suitable inhalational unit risk factor for carcinogenicity, a numerical WES is not recommended.

Based on the significance of the critical endpoint, further assessment of additional sources is recommended as a priority.

Recommendation for notations

Classified as a category 1B 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 due to evidence of dermal absorption and contribution to adverse systemic effects.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***NA***	***NA***
No report.		
ACGIH	***NA***	***NA***
No report.		
DFG	***2004***	***Not assigned***
MAK not assigned due to likely genotoxic mechanism of carcinogenicity. Considered carcinogenic in humans based on positive carcinogenicity in animals (category 2). Skin notation recommended, based on systemic effects in animals following dermal application. Summary of information: Metabolism to genotoxic epoxide derivative, which can alkylate macromolecules, demonstrated *in vivo*. Human data: • Formerly used as a sleep medicine, cancer therapeutic and solubiliser for analgesics (no further information provided). Animal data: • Adenocarcinomas in liver, small intestine, pancreas and lungs and haemangiosarcomas in liver at 250 mg/kg/d in chronic oral dose study (monkeys, 5 d/wk, 5 yr): ○ half of the exposed animals were irradiated with x-rays, irradiation had no effect on tumour type or incidence • Dose-dependent incidence of liver, lung and heart cancers in chronic drinking water study with dose groups 0, 2, 5.5 and 18 mg/kg/d (mice, 2 yr) • Non-mutagenic *in vitro* in bacteria and mammalian cell lines with or without metabolic activation; vinyl derivative was however strongly mutagenic under these conditions: ○ standard metabolic activation protocol does not produce appreciable amounts of vinyl metabolite, but its production occurs with human oxidative enzymes • Evidence of alkylated DNA and RNA derivatives found in liver following treatment with substance or epoxide metabolite (mice) • Positive results for micronucleus formation in bone marrow and peripheral blood reported in several studies following dermal application or IP injection (mice) • Chromosomal aberrations detected in embryos following maternal exposure at 1,280 mg/m^3 (mice, 48 h, GD 9–11). Insufficient data to recommend a sensitiser notation.		
SCOEL	***2012***	***Not assigned***
Summary of additional information: Classified as human carcinogen based on confirmed carcinogenicity in animals, supported by similarity in carcinogenic mechanism of action of vinyl chloride. Rodent and human metabolic pathways are similar and produce genotoxic carcinogenic metabolites. Not feasible to recommend a health-based TWA or STEL due to genotoxic carcinogenicity. Skin notation recommended based on carcinogenicity in dermally exposed animals.		

Source	Year set	Standard
Human data: • Nausea, vomiting and diarrhoea and leukopenia reported in leukemia patients receiving oral doses of 1–6 g/d, total doses: 26–390 g (n=32, 5–109 d) Animal data: • High acute doses (g/kg) used to induce narcosis in veterinary medicine: ○ minimum narcotic dose in mice of 2 g/kg • No data indicative of local irritation available • Decreased spleen and thymus weights and leukopenia at 4 mg/kg/d in repeat IP injection study (mice, 12 d) • DNA adduct-forming potency 2–4 fold higher than that of vinyl chloride, which has a similar genotoxic mechanism of carcinogenicity • Lower incidence of liver, heart and lung tumours in mice deficient in the oxidative enzyme implicated in the genotoxic mechanism of carcinogenicity • Increased mortality at 300 mg/kg/d in drinking water or 5% ethanol reported in subchronic feeding study (mice, rats, 13 wk); leukopenia observed at 20 mg/kg/d.		
OARS/AIHA	***NA***	***NA***
No report.		
HCOTN	***2000***	***Not assigned***

Summary of additional information:
No administrative OEL currently exists, available toxicological database is insufficient to recommend a health-based value. However, a health-based calculated occupational cancer risk value (HBC-OCRV) is estimated based on dose-response relationship of tumour incidence in mice estimated from results of a chronic feeding study. Lifetime oral unit carcinogenic risk factor is 0.35 $(mg/kg/d)^{-1}$ in mice. No differences in toxicokinetics are assumed between mice and humans, human inhalational unit risk factor therefore estimated at 0.018 $(mg/m^3)^{-1}$ assuming a respiratory volume of 10 m^3 during an 8 h shift in a 70 kg individual with a working lifespan of 40 out of 75 yr, working 48 wk/yr, 5 d/wk. An additional cancer risk of 4×10^{-5} is therefore predicted at an exposure of 0.002 mg/m^3.
Human data:
• None available.
Animal data:
• Genotoxic *in vitro* and *in vivo* based on positive results in several studies
• Demonstrated carcinogenicity in mice, rats and hamsters following oral, subcutaneous, IP or inhalational administration producing lung, liver, vascular and heart cancers
• Cancer risk assessment in humans based on chronic feeding study with dose groups 0, 0.1, 0.5, 2.5 and 12.5 mg/kg/d in drinking water (mice, rats, 2 yr):
  ○ increased incidence of mammary tumours at 2.5 mg/kg/d (female rats)
  ○ increased incidence of lung and mammary tumours at 0.5 mg/kg/d (male and female mice)
  ○ lifespan cancer risk estimated from linear extrapolation of dose-response relationship for tumour incidence in mice
  ○ oral unit carcinogenic risk factor under lifetime conditions estimated at 0.35 $(mg/kg/d)^{-1}$ (mice).		

Secondary source reports relied upon

Source		Year	Additional information

NICNAS	✓	2015	• Oxidative metabolism proceeds through 2 pathways:
			  ○ production of vinyl carbamate and corresponding epoxide, which both react with DNA
			  ○ production of ethanol and ammonia
			• Clearly genotoxic *in vivo* and *in vitro* based on several mutagenicity studies.

IARC	✓	2010	• Metabolised by CYP oxidative enzyme to vinyl carbamate and corresponding epoxide:
			  ○ this metabolic pathway is similar in rodents and in humans
			• Possible carcinogenic mechanisms include induction of DNA damage by its metabolites and an increased cell proliferation in target tissues
			• Sufficient evidence for carcinogenicity in animals:
			  ○ suggests similarities in the metabolic pathways in rodents and humans;
			  ○ formation of DNA-reactive carcinogens strongly suspected to cause cancer in rodents and would likely also occur in human cells
			• Overall evaluation: probably carcinogenic to humans (Group 2A).

NTP	✓	2016	• Polyurethane polymers used as foams, elastomers and coatings sometimes referred to as “urethane”: ○ these polymers are not made from the substance and do not generate it upon decomposition • Reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from numerous studies with rodents (mice, rats, hamsters).
US EPA	✓	1992	• Report archived, oral/inhalational unit risk factor and carcinogenicity not assessed.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?	Yes
Is the chemical carcinogenic with a mutagenic mechanism of action?	Yes

The chemical is a non-threshold based genotoxic carcinogen.

Is a cancer slope factor or inhalation unit risk value available?	No

Notations

Source	Notations
SWA	NA
HCIS	Carcinogenicity – category 1B

Source	Notations
NICNAS	Carc. Cat. 2
EU Annex	Carcinogenicity – category 1B
ECHA	Carcinogenicity – category 1B
ACGIH	NA
DFG	Carcinogenicity – 2, H (skin)
SCOEL	Carcinogenicity A, Skin
HCOTN	NA
IARC	Carcinogenicity – Group 2A
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:	
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%:	yes
	insufficient data to assign a skin notation

IDLH

Is there a suitable IDLH value available?	No, the chemical is a genotoxic carcinogen

Additional information

Molecular weight:	89.09
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 3.64 mg/m^3; 1 mg/m^3 = 0.27 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) (2004) Ethylcarbamat (Urethan) – MAK value documentation, German language edition.

European Chemicals Agency Regulation (ECHA) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH).

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2012) Recommendation from the Scientific Committee on Occupational Exposure Limits for Ethyl Carbamate [Urethane]. SCOEL/SUM/172.

Health Council of the Netherlands (HCOTN) (2000) Urethane (ethyl carbamate). Health based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2000/12OSH.

International Agency for Research on Cancer (IARC) (2010) Volume 96, Alcohol Consumption and Ethyl Carbamate. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2015) Carbamic acid, ethyl ester: Human health tier II assessment – IMAP report.

National Toxicology Program (NTP) (2016) NTP-RoC: urethane.

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).